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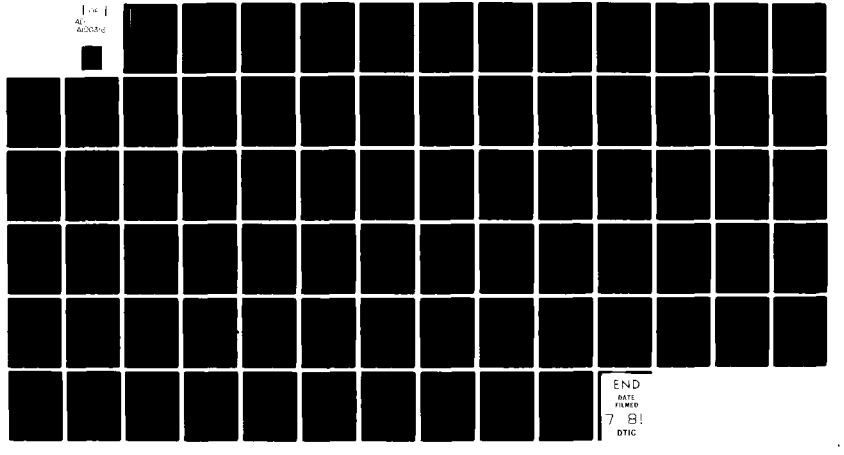

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Research and Development for Health and Environmental Hazard Assessment

TASK ORDER 1

DEVELOPMENT OF DATA BASE REQUIREMENTS FOR HUMAN HEALTH BASED WATER QUALITY CRITERIA FOR MILITARY RECYCLE/REUSE APPLICATIONS

FINAL REPORT

By:

Dr. Douglas Shooter
Dr. Rosalind C. Anderson

June 1980

Jointly supported by:

US Air Force Engineering and Services Center
Tyndall Air Force Base, FL 32403
(Air Force Technical Report No. ESL-TR-80-33)

Civil Engineering Laboratory
Naval Construction Battalion Center
Port Hueneme, CA 93043

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Fort Detrick, MD 21701
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Arthur D. Little, Inc.
Acorn Park
Cambridge, Massachusetts 02140

Project Officer: James C. Eaton, Jr.
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Fort Detrick, Frederick, Maryland 21701

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This report describes considerations for the derivation of water quality criteria for military recycle/reuse applications. Criteria based on human health effects must account for variation in subject exposure for different applications; the allowable daily dose must account for assimilation by ingestion, inhalation and dermal absorption.

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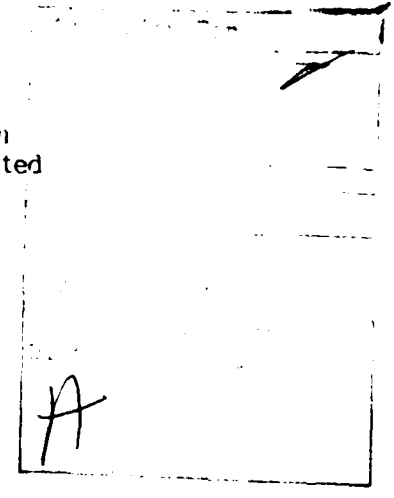

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EXECUTIVE SUMMARY

The development of a methodology for derivation of non-potable reuse water quality criteria can be divided into two segments:

- Determination of the daily allowable dose of a specific contaminant which produces no adverse health effects; and
- Estimating the concentration of contaminant in the recycled/ reused water which would cause the subject to assimilate the daily allowable dose, considering the total exposure received.

A first requirement is to assemble an adequate data base defining toxic effects.

Quantitative human toxicity data is normally compound specific, which suggests that each contaminant must be evaluated individually. Such a process would be essentially open ended; therefore a ranking should be made for chemical compounds. It should reflect their importance in specific recycle/reuse applications and their difficulty of removal by the wastewater treatment techniques under development by the military. When the ranking is established and agreed upon by a panel of experts, experiments to obtain missing toxicological data can be instituted. Much of the available human toxicity data is biased towards oral ingestion as the primary or sole route of entry. For non-potable recycle/ reuse applications, every potential route of entry, ingestion inhalation and absorption through the skin, must be evaluated (or re-evaluated). In tests using recycled water, potential effects from skin and eye irritation have been observed; data in this area are particularly scarce.

In many instances fully developed human toxicity data will not be available and cannot be conveniently and quickly established. Consequently it may be necessary to extrapolate from animal toxicity data or to use mathematical models, or to use worst case assumptions. Where such data are used it is advisable to critically evaluate their validity and use appropriate safety factors to compensate for uncertainty.

Another approach is to obtain toxicity data directly using effluent water samples or concentrates. This may identify toxic effects which are specifically sought, but not identify the compound causing the effects. It is particularly difficult to correlate toxicological effects with the engineering parameters (BOD, TOC, suspended solids, etc.) which are used to assess the efficiency of waste water treatment processes.

It is necessary to identify acceptable health based limits for specific contaminants appropriate to chronic, (1 year) sub-chronic (1 week to 1 year) and acute (1 week) effects. A toxicological protocol for extrapolation between these limits is not well established because the health effects of acute exposures may show a pattern different from those produced by chronic exposures.

Short term or emergency situations represent a particularly difficult case. Further work by the military is necessary to determine what additional adverse effects might be tolerable in emergency situations. Combat situations represent a special case and the potential level of adverse health effects which can be

tolerated will be different from that under other emergency (non-combat) situations. For these special situations it may be necessary to redefine the no-observable effects level (NOEL) and relax or tighten the criteria.

A second requirement is to develop an adequate data base to describe the subjects' exposure to recycle/reuse water.

Each application presents a characteristic but unique exposure pattern and for each case the importance of the various routes of entry (ingestion, inhalation, dermal absorption) will be different. For example, accidental ingestion may be significant during swimming activities but negligible during vehicle washing. The fraction of the body exposed and duration of exposure will also vary. Some experimental data exists, but it needs to be supplemented by a comprehensive evaluation of all the exposure characteristics for each potential recycle/reuse application. Variation among individual subjects and in different populations should be established.

Exposure characteristics need only be defined once for each application. The data can then be used to develop non-potable water quality criteria for any range of chemical species.

Mathematically, the methodology can be expressed in the following way:

No observable effects level (NOEL) = total allowable dose from all sources

= (uptake from food and drink)
+ (uptake from accidental ingestion)
+ (uptake from inhalation)
+ (uptake from dermal absorption).

or $(NOEL) = U_f + I + R + A$ (mg/day)

Where I, R and A are the uptake from ingestion, inhalation and dermal absorption respectively. Each of these terms is a function of the aqueous concentration of contamin ant therefore;

$$(NOEL) = U_f + C_p (I' + R' + A')$$

where C_p is the concentration of contaminant (mg/l) acceptable as the non-potable water quality criterion, and I', R' and, A' represent volumes of water.

This methodology is described in more detail in Chapter III following a review of recycle/reuse applications data in Chapter II. The available data and requirements for determination of exposure are discussed in Chapter IV and the requirements for evaluating toxicity data and associated health effects in Chapter V.

Our understanding of toxicological effects, particularly as they apply to recycle/reuse applications, is far from complete and the available data base is lacking in many important respects. The methodology proposed in this report is intended to serve as a set of guidelines for the development of non-potable water quality

criteria. We anticipate that it will be refined as more experience is gained concerning the sensitivity of the various parameters governing exposure and health effects and with the development of a comprehensive data base.

I. INTRODUCTION

The U.S. Army, Navy and Air Force all have programs for studying and implementing wastewater recycle or reuse in military applications. Many of these applications involve human contact with recycled or reused wastewaters; therefore, recycle/reuse systems must be designed and operated so as to minimize the possibility of adverse health effects from such contact. In order to develop, acquire and deploy military water treatment and distribution systems employing recycle or reuse of wastewaters, water quality criteria must be made available for each projected recycle/reuse application.

The applications of the military are often unique, populations may be narrowly defined, and emergency situations may exist in combat or training missions. The priorities of the military and the risks acceptable to the military are very much different from those of municipal authorities serving civilian populations and it will not suffice merely to adapt criteria that may be developed by the U.S. Environmental Protection Agency. The military must develop their own water quality criteria for military recycle/reuse applications. The Army Surgeon General has recognized two specific aspects of responsibility in the area of recycle/reuse: health criteria development relative to reuse, and attendant responsibility for aspects of nonmedical material that affect the health of personnel, such as water treatment, purification and distribution equipment. The Air Force Surgeon General and the Navy Bureau of Medicine (BUMED) have similar requirements.

The objectives of this study are to define the data base requirements for human-health-based water quality criteria, to develop a methodology for its application and to present the findings in a report which can be used by a panel of experts. The panel will use the findings to evaluate the adequacy of available toxicological and epidemiological data for setting non-potable water quality criteria for specific military applications of recycle or reuse.

Problems which will be encountered in the recycling of water will depend on the original use of the water, on the chemicals added to it during that use, on the treatment process designed to prepare the water for reuse, and on the precise conditions under which the water will be recycled. In order to define the limits of acceptable use, a methodology must be developed to assist in the assessment of human health hazards which might result from water reuse.

Unfortunately, there is not a long tradition of criteria development and validation for non-potable water as there is for drinking water. Thus, it is not possible to borrow directly from state or national criteria documents or standards. The State of California has made the greatest progress toward water reuse, but documents indicate this is generally with regard to irrigation or swimming, and coliform count has been the major concern. The problem of human health effects in agricultural applications is avoided by preventing human contact with water used for irrigation through the use of barrier zones and fences.

There are presently no useful models for establishing non-potable water quality criteria and standards. In the development of criteria for potable water, each chemical species is considered separately.

The categories of data listed in EPA water quality criteria documents as required for human health effects evaluation are Exposure, Pharmacokinetics and Toxicity. These same major categories of data will be required for non-potable, reused water evaluation. The criteria formulation, based on the weighting of the data, however, will be quite different for potable and non-potable water. For potable water data, oral administration is generally emphasized, and dermal or respiratory exposures are given little weight unless very severe effects are predicted. Evaluation of non-potable water places much more emphasis on data relating to effects resulting from dermal exposure, and respiratory exposure. In many recycle/reuse applications these become important routes of entry. For potable water, with an expected lifetime exposure, emphasis is placed on data which suggest chronic, progressive or irreversible changes resulting from exposure to waterborne chemicals. Human health data are highly valued but are extremely scarce, and carefully executed studies using rodents remain the main source of information.

Because of the special needs of the military population, data which demonstrate temporary and reversible changes in response to acute exposures will be deserving of more careful scrutiny than might be appropriate for a civilian population. Exposures to concentrations of irritant materials, which do not cause tissue damage or chronic changes, but which could induce degradation of performance in individuals would be detrimental or fatal to a combat mission.

Another type of data which may assume greater importance in the military setting is the allergenic potential of constituents of reused water. Allergic reactions are not usually life-threatening. However, if treatment is not available, if exposure is protracted, or if exposure is combined with poor personal hygiene, even modest skin lesions can have devastating importance.

II. RECYCLE/REUSE APPLICATIONS

A variety of treatment systems to provide reusable water from wastewater has been proposed, evaluated and in a few cases adopted by each of the armed services. The wastewaters studied include laundry and shower water[1], water from field hospitals[2], and mixed wastewaters[3]. This work has included extensive characterization of the wastewater before and after the specified treatment system in order to provide a good measure of the treatment efficiency for removal of various contaminents. For example, Table 1 shows the wide variety of constituents in shower wastewater as determined by one source in Reference 1. Since it is difficult to measure or control such a large variety of chemical species, it is desirable to concentrate on the more likely problem contaminants in order to measure the efficiency of the treatment system. This approach does not take into account the fact that removal efficiencies for different components are quite variable and may be unrelated to their health effects. Other studies provide data on industrial laundries,[4,5,6], coin operated laundromats[7], aircraft and vehicle wash racks, plating shops, cooling tower blowdowns,[3] etc. Table 2 gives an example of data for aircraft and vehicle wash racks. The emphasis is on the measurement of the conventional water quality parameters such as pH, alkalinity, total suspended solids, total dissolved solids, etc. and heavy metals. No information is given on specific organic compounds (except phenol) which would perhaps be most likely to cause adverse health effects in recycle/reuse applications.

A paper describing Army work on wastewater reuse within an Army field hospital[2] gives some interim reuse quality criteria developed by the Office of the Surgeon General[8], which are reproduced in Table 3. Principal control parameters proposed for the system were TOC and COD at levels of 5 and 10 mg/l, respectively. The paper discusses toxicity monitoring using a cytotoxicity test developed by Christian using mouse L cells. These cells are exposed for four days to continually replenished sample water containing growth media. Daily protein assays are made to determine growth inhibition brought about by toxic water samples. Toxicity levels and dose response relationships result from comparison with protein production of control cells. For some solutes, this cytotoxicity test has been shown to be several orders of magnitude more sensitive than all animal tests. The tests were applied to the partially treated wastewaters from the intermediate unit processes in the treatment train and could be characterized by their cytotoxicity removal efficiencies. One important finding was that the most toxic components in the RO permeate came from X-ray and laboratory wastewater. The toxic components were also found to be less effectively removed by the treatment system than were organic contaminants in general, indicating the inadequacy of TOC and COD measurements as indicators of Toxicity.

Toxicity studies were carried out as part of an evaluation of ultrafiltration as a technique for purifying laundry and shower wastes for reuse[9]. Tests were run with actual shower and laundry wastewater and also with more concentrated synthetic wastewaters simulating shower and laundry wastewater. To determine the safety of the recycled ultrafiltrate, a thorough toxicity and irritancy (dermal ocular and oral) study on mice and rabbits was conducted. All samples were evaluated with respect to their immediate toxicity in three ways: 1) when given orally to mice, 2) as a primary skin irritant when kept in contact with the intact and abraded skin of rabbits, and 3) as an irritant to the ocular tissue of the

TABLE 1

SHOWER WASTEWATER CONSTITUENTS

	mg/l
Silica Flour	100 - 210
Sodium chloride	60 - 180
Castor oil	20 - 130
Isopropyl alcohol	18 - 105
Ethanol	15 - 85
Kaolinite	20 - 50
Oleic acid	16 - 50
Talc	41
Tallow	13 - 38
Stearic acid	11 - 31
Coconut oil	9 - 30
Castor oil, sulfonated (75%)	6 - 30
Ultrawet 60-L	5 - 25
Ammonium lauryl sulfate	5 - 25
Sodium lauryl sulfate	5 - 22
Epithelium cells	18
N,N-Diethyl-m-toluamide	1- 15
sodium dodecylbenzenesulfonate	3 - 13
Sodium tripolyphosphate	5 - 11
Olive oil, sulfonated (75%)	2 - 10
Tannic acid	1 - 8
Triethanolamide alkylbenzene sulfonate (60%)	1 - 7
Potassium oleate (20%)	1 - 6
Kaloin, colloidal	5
Lactic acid	5
Triethanolamine	1 - 5
Urea	1 - 3
Glycerol	1 - 3
Potassium hydroxide	0.7 - 3
Zinc stearate	3
Coconut diethanolamine (92%)	0.5 - 3
Hair	2
Mineral oil	0.5 - 2
Potassium	1.5
Calcium carbonate	0.9
Aluminum hydroxide	0.9
Sorbitol	0.7
Dicalcium phosphate	0.6
Sodium-ortho-phenylphenolate	0.6
Sodium-4-chloro-2-phenylphenolate	0.5
Sodium metaphosphate	0.4
aluminum formate solution	0.4
Propylene glycol	0.3
Tricalcium phosphate	0.2
Volatile silicone	0.2
tegacid	0.2
Aluminum chlorhydrate	0.2
Tween 80	0.2

The following compounds are each present at < 0.2 mg/l

Ammonia
Aluminum Chloride
Aluminum sulfate
Ammonium alum
Beeswax
Boric acid
Cetyl alcohol
Corn starch
Bentonite
Hexachlorophene
Isopropyl myristate
Jamaican rum
Magnesium carbonate
Magnesium oxide
Glycerol monostearate
Methyl paraben
Lanolin
Petrolatum
PABA
Isopropyl palmitate
Polyethylene sorbitan monostearate
Saccharin sodium
Sodium-6-chloro-2-phenyl-phenolate
Sodium hydroxide
Sorbo
Spermaceti
Sorbitan monostearate
Stannous fluoride
Veegum
Zinc chloride
Sodium stearate

Source: Reference 1.

TABLE 2

QUALITY OF WATER FROM VEHICLE AND AIRCRAFT WASHDOWN

Constituent (Concentration mg/l)	VEHICLE WASH RACK		AIRCRAFT WASH RACK	
	Tolerable Input Quality[a]	Typical Effluent Quality[c]	Tolerable Input Quality[a]	Typical Effluent Quality[c]
BOD	20	450	20	5700
COD	50	1100	50	8400
Phenol	3.0	0.01	3.0	8.5
SS	20	(500)	20	470
TDS	2000	d	2000	d
Oil & Grease	10	110	10	280
Cl	600	d	600	d
NO_3	b	3.3	—	0.8
NH_4	15	(0.1)	15	(0.1)
PO_4	b	12	—	80
Na	600	d	600	d
$CaCO_3$	500	d	500	d
B	b	(0.1)	b	(0.1)
CN	0.5	(0.005)	0.5	(0.005)
Fe	40	2.6[d]	40	1.1[d]

a All concentrations estimated by contractor.

b Concentrations not significant for this activity.

c Concentrations in parenthesis are contractor estimates.

d Concentrations are strongly dependent on source water quality.

Source: Reference 3.

TABLE 3

INTERIM REUSE QUALITY CRITERIA FOR MUST WATER PURIFICATION ELEMENT COMPARED TO NATIONAL DRINKING WATER STANDARDS

Contaminant	Recomm. Limit	Maximum Allow	Interim Criteria for MUST WPE Reuse Quality (a)
Physical			
Turbidity, JTU	1(b)	5(b)	—
Color, PCU	15	—	50
Taste, Threshold	(e)	—	—
Odor, Threshold	3	—	—
Foaming	—	—	—
Total solids, mg/l	—	—	1500
Total Dissolved Solids, mg/l	500	—	—
Chemical, mg/l			
Total Organic carbon (TOC)	—	—	5(f)
Chemical Oxygen Demand (COD)	—	—	10(f)
Ammonia (NH_3)	—	—	0.5
Arsenic	0.01	0.05	0.05
Barium	—	1.0	1.0
Boron	—	—	—
Cadmium	—	0.01	0.01
Chloride	250	—	600
Chromium (Cr^{+6})	—	0.05	0.05
Copper	1	—	1.0
Cyanide	0.01	0.2	0.2
Fluoride	0.7-1.2	1.4-2.4	4.0
Lead	—	0.05	0.05
Magnesium	—	—	150
Mercury	—	0.002(b)	—
Nitrate-Nitrogen	—	—	10.0
Oxygen, Dissolved	—	—	—
Selenium	—	0.01	0.01
Silver	—	0.05	0.05
sulfate	250	—	400
Alkyl Benzene Sulfonate	0.5	—	0.5
Iron	0.3	—	0.3
Manganese	0.05	—	0.05
Phenols	0.001	—	0.001
Zinc	5	—	—
$CHCl_3$ Extract (c)	0.2	—	0.2

a Office of the Surgeon General, U.S. Army (see Reference 8)
b Interim Primary Drinking Water Standards, Federal Register, 40(51)Part II, 14 March, 1975.
c Organic contaminants
d Not applicable
e None objectionable
f Tentative maximum

Source: Reference 4.

rabbits. The treated wastewater caused no irritation to the skin or eyes of rabbits and showed no measurable oral toxicity. Untreated shower and laundry wastes containing up to 8,000 mg/L of organic carbon, such as 100 times concentrated raw shower waste, did show a mild irritant reaction. Similarly, a concentrated (untreated) solution containing 70,000 mg/L of TOC was one of the few which showed significant eye irritation. Only laundry wastewater samples which contained greater than 2,500 mg/L TOC were irritating to the eye. These samples were also found to be non-mutagenic in microbioassays.

A limited comparison of the animal tests was made with human volunteers[10], with the results shown in Table 4. The limited human data tend to support the conclusions from animal tests that treated shower water does not causes adverse health effects. However, it was shown that highly concentrated raw wastewater i.e., 100 times for both shower and laundry wastewaters, did produce toxic responses in oral toxicity tests with mice. The LC_{50} value (TOC) for shower wastes was 2.4 gm/kg and the LC_{50} value for laundry wastes was 2.7 gm/kg. This result clearly indicates the need for defining criteria in terms of individual chemical contaminants.

A recent report[1] evaluating the reuse of laundry and shower wastewater identified approximately 100 different chemical compounds and attempted to document toxicity data for these compounds. It was concluded that the toxicity data did not indicate any human toxic response would be expected from short term shower or laundry water reuse by Army field units. However, complete toxicity data were lacking for at least the 36 compounds shown in Table 5. From an appraisal of the toxicity data it was concluded by the authors that ocular toxicity is probably the most sensitive human endpoint in this application. They also concluded that a large data gap occurred with regard to ocular toxicity of the pure chemical as a function of concentration and exposure times. Another gap that was noted was the lack of data on dermal sensitization and photo-sensitization. (The following chemical constituents of Army field showers and laundries have been shown to cause dermal sensitization: nickel, protease, parabens, lanolin, propylene glycol, triethanolamine, sorbic acid, and hexa-chlorophene.)

In evaluating the health effects due to shower water reuse in this work, it was assumed that the ocular and dermal exposures are of several minutes duration, and that oral exposures are minimal, amounting to only a few ml of recycled water per shower. The consequences of ocular toxicity can be very serious to the individual and to a unit's combat readiness; therefore, good estimates of human ocular toxicity for recycled wastewater are important. Conversely, the minimal oral exposure suggests that highly precise oral toxicity data may not be required for this application.

TABLE 4

TYPICAL IRRITATION RESPONSES OF SHOWER AND LAUNDRY WASTEWATER

Sample	CONCENTRATION: Total Organic Carbon, mg/l	CONCENTRATION: Total Solids, mg/l	Irritation † (Rabbits): Skin	Irritation † (Rabbits): Eye	Skin Irritation Behavior # (Human)
Shower					
Synthetic* 500 x (filtered, 0.45 μ)	28,000	47,000	Corrosive	3	—
Synthetic 200 x (filtered, 0.45 μ)	4,942	9,500	3.0	1	—
Synthetic 100 x (raw)	8,167	20,800	3.6	0	Irritating
Synthetic 50 x (filtered, 0.45 μ)	1,556	2,174	1.1	1	—
Actual+ concentrate stream from UF unit	1,427	4,020	0.6	0	No irritation
Actual 7th pass ultrafiltrate	200	727	1.6	0	No irritation
Actual + urine (ultrafiltrate)	51	280	0.8	0	No irritation
Tap water	3	180	0.4	0	No irritation
Laundry					
Synthetic 500 x (filtered, 0.45 μ)	72,000	248,000	5.4	6	—
Synthetic 100 x (filtered, 0.45 μ)	2,613	72,340	3.5	4	—
Synthetic 50 x (filtered, 0.45 μ)	800	28,000	2.6	0	Irritating
Synthetic 10 x (ultrafiltrate)	50	4,800	0.8	1	—
Synthetic 75 x with Army type 1 detergent (filtered, 0.45 μ)	2,370	55,000	1.2	0	No irritation

* synthetic = totally fabricated wastewater
+ actual = true wastewater modified by chemical addition to resemble the synthetic wastewater
# as determined by closed patch tests (see reference 10).
† as determined by criteria described in reference 10
Source: Reference 9.

TABLE 5

COMPOUNDS FOR WHICH TOXICITY DATA ARE NOT AVAILABLE

COMPOUND	ORAL	SKIN	EYES
Aluminum chloride			X
Aluminum formate			X
Aluminum hydroxide			X
Aluminum sulfate			X
Bentonite			X
Castor oil			X
Cetyl alcohol	X		
Corn starch			X
Dicalcium phosphate			X
Ethoxylated lauryl alcohol	X	X	X
Glycerol monostearate	X	X	X
Isopropyl myristate			X
Isopropyl palmitate	X		X
Lanolin			X
Magnesium carbonate			X
Magnesium oxide			X
Methyl paraben			X
Potassium oleate			X
Polyethylene sorbitol monostearate			X
Propoxylated PABA			X
Sodium-4-chloro-2-phenyl phenolate	X		X
Sodium-6-chloro-2-phenyl phenolate	X		X
Sodium dodecyl benzene sulfonate	X		X
Sodium ortho-phenyl phenolate	X		X
Sodium saccharin			X
Sodium silicate			X
Sodium stearate			X
Sodium sulfate			X
Sorbitol			X
Spermaceti	X	X	X
Sulfonated Caster oil	X	X	X
Tegacid	X	X	X
Tricalcium phosphate			X
Veegum	X	X	X
Whitening agents	X	X	X
Zinc stearate			X

(X indicates toxicity data are not available)

Source: Reference 1.

III. DERIVATION OF HEALTH BASED WATER QUALITY CRITERIA

A. Proposed Methodology for Systemic Intoxications

The starting point for the development of criteria is to determine the maximum daily uptake which has no observable health effect. Methods to determine the maximum allowable daily uptake and the factors which contribute to it are described in detail in Chapter V. This no observable effect level (NOEL) in mg/day) is the maximum amount that can be tolerated from all sources. It should incorporate appropriate safety factors which are conditioned by the type and quality of data used in the calculation. Different values for the NOEL will also be assigned to fit acute, subacute and chronic situations. Described mathematically:

NOEL(mg/day) = Total daily dose from all sources.

= (uptake from injestion) + (uptake from respiration) + (uptake from dermal absorption)

$$= I + R + A$$

Total uptake from ingestion must include the amount consumed in food and drink (U_f) in addition to any incidental ingestion (U_i) characteristic of the particular reuse application.

$$I = U_f + U_i$$

Uptake from respiration may be as vapor (U_v) or as mist (aerosol) (U_m) depending on the volatility of the contaminant and the characteristics of the activity.

$$R = U_v + U_m$$

Uptake via dermal absorption can take place by solution (U_n) or a preferential mechanism (U_p). The solution mechanism occurs when the contaminant is absorbed through the skin at the same rate as water. The preferential rate occurs when the contaminant is absorbed more rapidly than water.

$$A = U_n + U_p$$

Except for the uptake from food and drink (U_f) all the uptake factors are a function of the pollutant concentration C_p in the non-potable water; therefore,

$$NOEL = U_f + C_p (U'_i + U'_v + U'_m + U'_n + U'_p)$$

Where U' now have the dimensions of volume (liters of water).

The relevant water quality criteria can now be obtained by rearranging the equation in terms of C_p i.e.,

$$\text{Water Quality Criteria} = C_p = \frac{NOEL - U_f}{(U'_i + U'_v + U'_m + U'_n + U'_p)}$$

For some applications the equation may be simplified. If accidental ingestion is

negligible, $U'_i = 0$. If the contaminant is non-volatile $U'_v = 0$.

Each term U', is a function of the exposure created by the particular activity being considered, and can be described by the rate of assimilation of the pollutant (R) and duration of the exposure (t).

$$U' = f(R,t)$$

Details of the exposure characteristics for different types of activity which may in the future be candidates for recycled water are described in Section IV.

B. Illustrative Examples

The data requirements to use the methodology are:

1. Toxicological data to determine the NOEL

2. Exposure data (route and duration) for each activity.

Experimental data may be available from one or more sources, or if unavailable an estimate may be made. A basis for data selection can be provided by the following hierarchy.

For NOEL:

1. Toxicological data from human health studies.
2. Toxicological data from animal studies.
3. Extrapolation from data for similar chemicals.
4. Mathematical models.
5. Worst case estimate

For Exposure:

1. Experimental data for proposed recycle/reuse activities.
2. Extrapolation from related experimental data.
3. Mathematical models.
4. Worst case estimate.

To further simplify the proceedure it is suggested that certain limiting assumptions be made to permit the development of interim water quality criteria in the absence of a complete set of experimental data. For example:

> *No health criteria for a contaminant need be more restrictive than the criteria adopted for potable water standards.*

If the contaminant in question is not typically present or can be efficiently removed by a wastewater treatment system, the interim criteria can be set at the level for potable water and eliminate the need for further experimental data.

Levels of contaminants typically found in effluents from a particular application shall be acceptable in recycle situations if no adverse health effects have been observed in extensive and extended exposures.

For example, the concentration of detergents typically used in laundry applications has not been shown to have any adverse health effects from experience in a wide range of installations. This generalization would not be applicable to reuse applications, for example reuse of laundry water as shower water.

Primary emphasis in determination of toxicity data should be given to those constituents in the wastewater which are difficult to remove in the treatment processes, normally employed for the intended use.

For example, a recent study has identified seven contaminants in shower water and four contaminants in laundry water which fall into the "difficult to remove" category. These data are summarized in Table 6. Some toxicity data exist for each of these compounds but more information is needed with respect to skin absorption and eye irritation.

A suggested format for presentation of the data and calculation of criteria levels is shown in Table 7. It defines the input parameters necessary to apply the method for a specific contaminant and activity. The source of the data and the basis for the estimate are given to allow an assessment of the reliability of the final answer. Three example calculations are presented on the following pages to demonstrate the use of methodology. The contaminants phenol, cyanide, and hexachlorophene (HCP) were chosen because relevant data were available and are intended to be illustrative only.

TABLE 6

CONCENTRATIONS OF PROBLEM CONTAMINANTS IN TREATED WASTEWATER PRIOR TO REUSE

(90% Conversion)

Wastewater Source	Contaminant	Typical Effluent Concentration (mg/liter)	Stationary Concentration in Output from Treatment System (1) mg/liter			
			UF-RO	UF	ACA-IX	ERDLator
Shower	Ethanol	84	100	280	240	410
	Isopropanol	105	10	114	71	180
	Glycerol	2.8	0.4	3.3	3.0	7.6
	Lactic acid	5.0	1.9	8.5	2.1	5.0
	Triethanolamine	7.5	0.5	7.5	1.8	5.7
	Urea	3.0	3.0	8.5	9.8	20
	Sodium chloride	180	2.0	150	2.4	1,600
Laundry	Ethanol	1.4	1.7	4.7	3.9	6.8
	Urea	13	13	37	42	87
	Sodium carbonate	533	0.0	436	0.0	4,800
	Sodium sulfate	112	1.3	95	1.5	1,000

1. Treatment Systems are: UF-RO = ultrafiltration, reverse osmosis
UF = ultrafiltration
ACA-IX = filtration, activated carbon adsorption, ion exchange
ERDLator = powdered carbon and polyelectrolyte addition, chlorination and filtration.

Source: adapted from Reference 1.

TABLE 7

FORMAT FOR CALCULATION

Name of Contaminant:
Activity: Activity Classification: (acute, sub-acute, chronic)

Parameter	Value Assumed	Source	Basis for Data
NOEL	(mg/day)		
EXPOSURE DURATION	(minutes)		
EXPOSURE ROUTES			
Ingestion	(liters)		
Inhalation - vapor	(liters)		
- mist	(liters)		
Dermal Absorption			
- solution	(liters)		
- preferred	(liters)		
Uptake from food and drink	(mg/day)		
ADDITIONAL SAFETY FACTORS			
Population			
Activity Classification			

CALCULATION

Non-potable water quality criteria for = mg/l.

Example 1

Scenario

In a remote area where swimming is the main recreational activity available to the troops it is observed that individuals swim up to 2 hours/day. The swimming facility is fed from a treated wastewater stream contaminated with phenol. What concentration of phenol may be allowed in the swimming water without exceeding the NOEL?

Name of Contaminant: Phenol
Activity: Swimming Activity Classification: chronic

Input Data

Parameter	Value Assumed	Basis for Data Selection
NOEL	7 mg/day	EPA Water Quality Criteria (Ref. 11)
EXPOSURE DURATION	2 hrs/day	Actual observation
EXPOSURE ROUTES		
Ingestion	U'_i = 100 mL	Estimate from Ref. 12 (see note 1)
Inhalation vapor	$U'_v = 1.22 \times 10^{-3}$ liters	Vapor pressure = 0.35 mm Hg. Worst case assumption (see Note 2)
Mist	negligible	Assume no mist for this activity
Dermal absorption	$U'_n = 1.8 \times 10^{-2}$ liters	Assume that phenol is absorbed in solution (i.e., no preferential absorption (see note 3)
Uptake from food and drink	U_f = 1.226 mg/day	Assume that drinking water meets criteria for protection of aquatic life 0.6 mg/l. Ref. 13 (see note 4)
ADDITIONAL SAFETY FACTORS		
Population	1.0	Assume general population
Activity classification	1.0	Based on source of NOEL

CALCULATION

Total phenol dose from swimming = $U_f + U_i + U_v + U_n$

$$\therefore \text{(NOEL) } 7 \text{ mg/day} = 1.226 + C_p\,(0.1 + 0.0012 + 0.018)$$
$$7 = 1.226 + C_p\,(0.1192)$$
$$C_p = 48 \text{ mg/l.}$$

The swimming pool water may contain up to 48 mg/l of phenol without exceeding the NOEL. In this example 75% of the dose is obtained from the accidential ingestion; therefore a good estimate of this parameter is important.

NOTE 1

The amount ingested during swimming is not well documented and probably highly variable. A value of 100 ml has been assumed, based on an estimate by Culp.

NOTE 2

The vapor pressure of phenol P_{vp} is 0.35 mm Hg at 25°C. (Ref. 14)

Assume that 100% of the vapor inhaled is absorbed.

Assume that swimming is strenuous activity with a respiration rate (minute volume) of 30 liters/min.

then Amount Inhaled in vapor U_v (see Appendix D) $= P_{vp}.C_p \times 9.7\times10^{-7} \times 30 \times 120$

$$= C_p \times 1.22\times10^{-3}$$

NOTE 3

Assume that phenol is absorbed concurrently with water (i.e., no preferential absorption, $U_p = 0$).

Reference 15 estimates that transport of water through the skin is 0.5 mg/m^2/hour.

Body surface area = 18,000 cm^2, Fraction exposed during swimming, 1.0.

$$U_n = C_p \times 0.5 \times 10^{-6} \times 18{,}000 \times 2$$

$$U_n = C_p \times 0.018$$

NOTE 4

Based on the protocol used in Ref. 13 (see page 29 of this report) with a drinking water concentration of 0.6 mg/l phenol amount ingested from fish = 0.026 mg/day, amount ingested from drinking water 1.2 mg/day; total = 1.226 mg/day.

Example 2

Scenario

A base in a water short area wishes to use a treated waste water stream for washing vehicles. This stream is derived in part from industrial wastewater which contains cyanides. What is the maximum concentration of cyanides which can be tolerated.

Name of Contaminant: Cyanide ion (CN^-)
Activity: Vehicle washing Activity classification: chronic

Input Data

Parameter	Value Assumed	Basis for Data Selection
NOEL	8.4mg/day	EPA Water Quality criteria Ref. 11
EXPOSURE DURATION	8 hour/day	Typical work schedule
EXPOSURE ROUTES		
Ingestion	negligible	Assume good occupational health and safety standards
Inhalation		
Vapor	U'_v = 4.25 liters	Vapor pressure = 760 mm Hg Ref. 14 Worst case estimate (see Note 1)
Mist	U'_m = 0.0029 liters	Worst case estimate (see Note 2)
Dermal absorption	U'_n = 0.0144	Assume cyanide is absorbed by solution (see Note 3), Worst case estimate
Uptake from food and drink	U_f - 2.86 μg/day	Uptake from food and drink negligible, (see Note 4)
ADDITIONAL SAFETY FACTORS		
Population	1.0	Assume general population
Activity classification	1.0	Based on source of NOEL

CALCULATION

Total cyanide dose from vehicle washing = $U_v + U_m + U_n$

$\therefore$ (NOEL) 8.4 mg/day $= C_p\ (0.0029 + 4.2 + 0.0144)$

$= C_p\ (4.2573)$

$C_p = 1.97$ mg/l

The maximum allowable cyanide concentration is 2 mg/l. Practically all the cyanide is assimilated as vapor.

NOTE 1

Vapor pressure of hydrogen cyanide is 760 mm at 25°C. (Ref. 14)

Assume that 100% of the vapor inhaled is absorbed.

Assume that vehicle washing is moderate activity with a respiration rate (minute volume) of 12 liters/min.

then amount inhaled in vapor $U_v = P_{vp}.C_p \times 9.7\times10^{-7} \times 12 \times 480$
(see Appendix D)

$U_v = C_p \times 4.25$

NOTE 2

Assume that the water content of the mist is 5×10^{-3} ml/liter (see page 29)

Assume all particles are of respirable size and 100% are retained

Respiration rate is 12 liters/min.

then amount inhaled in mist $U_m = C_p \times 5 \times 10^{-7} \times 12 \times 480$

$U_m = C_p \times 0.0029$

NOTE 3

Assume that cyanide is absorbed concurrently with water and not preferentially.

Assume a maximum rate of water transport through the skin of 0.5 mg/cm^2/hr.

Body surface area = 18,000 cm^2, fraction exposed = 0.2

Amount absorbed through the skin $U_n = C_p \times 0.5 \times 10^{-6} \times 0.2 \times 8$

$U_n = C_p \times 0.0144$

NOTE 4

Based on the protocol used in Ref. 13 (see page 29 of this report) and a water criteria concentration of 1.4 μg/liter, amount ingested from fish = 0.26 μg/day, from drinking water 2.8 μg/day.

Example 3

Scenario

In an arid area, shower water is being recycled to conserve potable supplies. The treatment system is not completely effective for the removal of hexachlorophene (HCP) which is added as a bactericide. What is the maximum level of HCP which can be tolerated?

Name of Contaminant: Hexachlorophene
Activity: shower Activity classification: chronic

Input Data

Parameter	Value Assumed	Basis for Data Selection
NOEL	3.0 mg/day	Based on information in Ref. 1 (see Note 1)
EXPOSURE DURATION	15 minutes	Based on information in Ref. 27
EXPOSURE ROUTES		
Ingestion	U'_i = 0.018 liters	Based on Ref. 16
Inhalation		
Vapor	negligible	
Mist	U'_m = 2.25 x10^{-4} liters	Worst case assumption (see Note 2)
Dermal adsorption	U'_m = 2.25x 10^{-3} liters	Worst case assumption (see Note 3)
Uptake from food and drink	negligible	
ADDITIONAL SAFETY FACTORS		
Population	1.0	General population (see Note 4)
Activity classification	1.0	Based on source of NOEL

CALCULATION

Total HCP dose from shower = $U_i + U_m + U_n$

$$\therefore \text{(NOEL) } 3.0 \text{ mg/day} = C_p\ (0.018 + 2.25\times10^{-4} + 0.0011)$$
$$= C_p\ (0.0193)$$
$$C_p = 155 \text{ mg/l}$$

The maximum allowable level of HCP to protect normal population during showering is 155 mg/l.

NOTE 1

The NOEL is based on a value for human TDL_o = 43 μg/kg, quoted in Ref. 1. Assume a 70 kg person this translates to a NOEL of 3.0 mg/day. The NOEL calculated in this manner is more restrictive than one based on LD_{50} data.

NOTE 2

Assume that the water content of the mist is 5×10^{-3} ml/liter (see p. 29).

Assume all particles are of respirable size and 100% are retained.

Respiration rate is 6 liters/min (light activity).

HCP inhaled in mist $U_m = C_p \times 5 \times 10^{-7} \times 6 \times 15$
$= C_p \times 2.25 \times 10^{-4}$

NOTE 3

Assume that HCP is absorbed concurrently with water and not preferentially.

Assume a maximum rate of water transport through the skin of 0.5 mg/cm^2/hour.

Body surface area 18,000 cm^2 fraction exposed 1.0

Amount absorbed through the skin $U_n = C_p \times 0.5 \times 10^{-6} \times 18{,}000 \times 0.25$
$U_n = C_p \times 1.12 \times 10^{-3}$

NOTE 4

Some individuals may be dermally sensitive to HCP, but the value of NOEL is based on the oral TDL_o of 43 μg/kg. The value for child skin TDL_o is 300 mg/kg. Therefore a normal population has been assumed.

IV. DETERMINATION OF EXPOSURE

The primary factors which determine exposure are:

- Exposure Route
- Exposure Duration
- Population Exposed

Each of these factors is the sum (or product) of a number of elements which are summarized in Table 8.

Human exposure to recycle/reuse water will be specific for each application, but variations will occur between individuals associated with the activity due to variations in duration of exposure and population.

A. Exposure Routes

1. Ingestion

Accidental ingestion is likely to be significant in some applications such as swimming and showering and may be negligible in other applications such as vehicle washing. There are no actual measurements and few estimates in this area. Where ingestion is expected to be minor, an order of magnitude estimate should be sufficient.

Uptake of contaminant from food and drink may add significantly to the total dose. The EPA[13] has developed a protocol used in the determination of potable water quality criteria which estimates the amounts of contaminant assimilated by this route. It is assumed by EPA that water consumption is 2 l/day and that daily fish or shellfish consumption in the United States is 18.7 grams per person per day. There is a tendency for some types of fish to accumulate pollutants such that the edible portion of the fish contains more of the pollutant than would be predicted on the basis of equilibrium with the ambient water. To account for this result, a bio-concentration factor is also included in the calculation. The contribution from food and drink will be small for some contaminants which are not normally found in the environment. For others, especially if the potable water is of low quality, the contribution may be large.

2. Inhalation

Inhalation of contaminants can occur by two mechanisms: inhalation of vapors in equilibrium with the contaminated water or inhalation of a mist (aerosol) of water droplets which may be associated with various reuse activities. Compounds with high vapor pressure e.g., chloroform or benzene may result in an appreciable dose from inhalation of vapor, but for low vapor pressure compounds such as phenol or chlorinated pesticides ($<$ 1mm Hg at 25^{o}C) even continuous exposures by inhalation of vapors would be insignificant. Vapor pressure increases rapidly with temperature; therefore for activities involving elevated water or ambient temperatures, inhalation of vapors would be of greater concern. In addition to breathing vapor, persons may, in some activities, be exposed by breathing mist generated from polluted water sources. The quantity of contaminant contained in the mist is proportional to the number and size

TABLE 8

SUMMARY OF DATA REQUIRED FOR A COMPLETE DESCRIPTION OF EXPOSURE

	Primary Elements	**Secondary Elements**
A. EXPOSURE ROUTES		
1. Ingestion	Concentration in water Volume ingested Uptake from food and drink	pH of water Stability in acids
2. Inhalation	Concentration in water Respiration rate	Lung irritation or damage
• vapor	Concentration in air	
• mist (aerosol)	Concentration in mist	Particle size distribution
3. Dermal Absorption	Concentration in water Fraction of body surface exposed Mechanism of adsorption	Reaction with skin Effects of skin damage Synergistic effects of solvents Water temperature
B. DURATION OF EXPOSURE		
	Duration of each exposure Frequency of exposure	Level of stress
C. POPULATION EXPOSED		
	Health Age Sex	High risk groups: wounded, sick, pregnant children, elderly, allergic, obese, smokers

distribution of droplets in the mist and the concentration of pollutants. In mists formed by condensation, the concentration of pollutant in the droplets may be more or less than in the original contaminated water because of fractionation. For mechanically formed mists e.g., those which might be generated during showering or vehicle washing, the concentration of pollutant in the droplets would be approximately that in the original source.

A determination of particle size and particle size distribution is necessary to accurately predict deposition in the respiratory tract[17]. The greatest alveolar deposition occurs in the 1- to 2- μm range and then decreases to a minimum at approximately 0.25 μm. Below 0.25 μm, alveolar deposition again increases due to Brownian movement. Approximately 82% of 1.0μm particles, 28% of 0.1 to 0.3 μm particles and 51% of 0.03 μm particles are deposited in the broncheoles or the alveoli. (This aspect of aerosol deposition becomes particularly significant when viral size particles [about 0.01 to 0.1 μm] are considered.)

Particles having an effective diameter larger than 10 micrometers are excluded from the respiratory tract and therefore cannot produce toxic effects in the lung. Very small particles are very likely to be exhaled during normal respiration since they do not have sufficient weight to cause impaction at inflextion points or deposition resulting from gravity. Thus, the measured concentrations, of mist may overestimate the exposure.

Information about the distance between aerosol source and the exposed population may also be necessary. The spread of aerosols by wind or air currents can cover remarkably long distances. Irrigation with wastewater in one instance was shown to distribute viable coliform bacteria a distance of 350 meters downwind form the source of the spray[18]. The calculation of exposure indicated that at a distance of 100 meters, a worker would inhale 36 bacteria in each 10 minute period. (The degree of contamination of the original water was not specified.) The longest distance for estimated dissemination of microbiological particles was .8 miles. The viability at such a distance depends on humidity, ultraviolet radiation, wind speed, and specific type of virus or bacterium.

3. Dermal Absorption

The process of absorption through the skin results from a combination of absorption into the stratum corneum, i.e., the dead surface layer of the epidermis, and diffusion through the underlying skin layers into the microcirculation. Although the skin's diffusivity and thickness varies with location on the body, the steady state permeability and flux through normal skin remains relatively constant. A few regions of the skin are exceptionally permeable (forehead, palms, soles and scrotum) and will allow more rapid access of contaminants than would otherwise be expected. The high permeability of the palms of the hands is especially significant for most potential military applications. Another sensitive area is the eye, where irritation has been noted in potential water reuse studies,[9] and absorption characteristics are quite different from those of the skin generally.

Diffusion through the stratum corneum is considered to be the rate limiting step, and may result from one or both of two mechanisms:

1. Diffusion concurrent with solvent transport, or

2. A combination of preferential adsorption on the stratum corneum and diffusion through it.

Estimates of skin permeability to water range from 0.2 to o.5 mg/cm^{2}hr[15,25]. Use of this data allows a calculation of absorption by the first mechanism. The second mechanism implies preferential absorption and is more difficult to assess because of the lack of data. A mathematical model based on a preferential absorption mechanism is presented in detail in Appendix A.

A key variable is probably the membrane (skin) /water partition coefficient. Unfortunately, only limited data are available, although there is some evidence to suggest that those compounds with a high mineral oil/water or high octanol/water partition coefficient also have a high permeability constant through the skin. Skin absorption occurs in proportion to the area of skin in contact with the water being used; therefore, the extent of skin exposure must be determined for each water reuse situation. Data are available from scientific tables[26] which allow us to describe the surface area of various parts of the body in terms of the percent of the total. For example, hands and lower arms constitute approximately 10% of the total, as do face and neck. For some applications, the extent of exposure can be readily estimated. Total exposure (100%) would occur during swimming or showering. About 20% of the body would be exposed (face, neck, hands, and lower arms) in some sorts of equipment washing procedures. Other exposures might involve more limited contact e.g., clothing wet only in the front — or from the knees down. The surface area in contact with such water can be determined fairly easily.

B. Duration of Exposure

Duration of exposure varies considerably for different applications. Activities such as swimming may take place infrequently; showers take place regularly, but there is a wide range of individual exposures. Occupational exposure e.g., vehicle washing will extend throughout the normal workday.

Single or multiple exposures may be involved. The single exposure would presumably occur only in an emergency. The appropriate health evaluation of single exposure situations would be with reference to acute toxicity data which relate to four days (96 hours) exposure. Multiple exposures for periods of from 5 days to one year and for periods greater than one year, would by contrast, require subchronic or chronic toxicity data for prediction of health effects.

It is important that the frequency of exposure and the dose at each exposure be examined if possible as discrete elements in the evaluation of exposure. For example, oral intake of a toxic material of 1 gram/day for thirty days is not equivalent to a 30 gram dose in a single occurrence.

C. Population Exposed

The population exposed to a water reuse source should also be evaluated in order to predict human health effects. Special subgroups which might exist are:

1. healthy young males
2. healthy young females
3. pregnant females
4. fetus
5. infant, children
6. individuals with acute or chronic disease
7. individuals with idiosyncratic high sensitivity
8. individuals with allergies
9. elderly

In any permanent military installation a complete spectrum of the population will probably be represented at risk. The inclusion of females in virtually all military activities adds the unavoidable possibility of a population containing pregnant females and fetuses, both of whom are more sensitive to some water contaminants. Infants, children and elderly persons can be excluded from many but not all exposures of military importance. A particular problem with children, in addition to increased sensitivity during growth, is their different set of behavioral standards compared to adults. Some military populations are clearly limited e.g., on board ship, combat and combat training exercises. However, injured personnel may be considerably more sensitive to exposure. It is always difficult to protect against idiosyncratic sensitivity or allergic individuals. These conditions can seldom be identified before an exposure of sufficient dimensions causes adverse reaction.

D. Data Available for Estimating Exposure

1. Applications

A number of potential military recycle/reuse applications have been identified[20] which are listed below:

Source/Use	Type of Installations
Laundry/Laundry	Field and Fixed
Shower and washroom/Shower and washroom	Field and Fixed
Miscellaneous/Swimming	Fixed
Miscellaneous/Irrigation	Fixed
Miscellaneous/Dust Control	Field and Fixed
Miscellaneous/Engineering construction	Field and Fixed
Miscellaneous/Aircraft Washing	Field and Fixed
Miscellaneous/Industrial uses (cooling towers, boilers, scrubbers, washracks, painting, machine shop)	Fixed
Miscellaneous/Turbine Washing	Field and Fixed
Miscellaneous/Hospital	Field and Fixed

The miscellaneous sources may include wastewater from base housing, aircraft washing, cooling towers, boilers, scrubbers, washracks, machine shop, turbine washing, and swimming activities.

Shower and laundry water represent a large portion of the wastewater generated in field and in fixed installations and therefore these applications have a

relatively high priority. It can be anticipated that the characteristics of recycle/reuse applications for laundry and shower water will be similar in character from one installation to another at fixed installations. Under field training and combat situations this may not hold true because of additional contamination. Differences in demographics of population exposed and time of exposure also suggest that different criteria might be required for fixed and field installations.

Table 9 illustrates some of the variations in exposure characteristics which represent different activities. Data available for calculation of each of these parameters are summarized below.

2. Exposure Routes

There are few data to quantify incidental ingestion. Culp[12] has estimated a value of 18 ml for ingestion during showering. 100 ml has been assumed for ingestion during a 2 hour swim. Ingestion from food and drink can be estimated using the EPA protocol[13] which assumes a daily intake of two liters of water and 18.6 grams of shellfish. For some contaminants a bioconcentration factor is also applied, e.g., for phenol and cyanide the bioconcentration factor is 2.3. As a first estimate for calculation it may be assumed that the concentration of contaminant in the drinking water is at the criteria limit set for the protection of aquatic life. Absorption of ingested water by the gut is very efficient and an assumption of 100% absorption is justified.

Vapor pressure of volatile contaminants in water can be approximately estimated using Henry's Law[21] which states that the partial pressure of the solute in the gas phase is directly proportional to the concentration in the solution. Appendix D derives a form of this equation applicable to this situation.

There are no available data on particle size and particle size distribution for mechanically formed mists appropriate to the activities under consideration. One source[22] indicates that a fog contains between 5-30 grams of water particles/m^3 of air. There are no estimates of the amount of inhaled mist which is retained; in the absence of data it is appropriate to use 100% retention as a worst case estimate.

Data on ventilation rates for persons performing various activities are available from the literature[23] and vary from 30 liters/min. for strenuous exercise (e.g., swimming) to 6 liters/min. for sedentary activity (e.g., showering, shaving).

Dermal exposure is related to the surface area of skin which can be affected. The total surface area of the skin is related to body weight and height and can be determined using the freely available nomogram as published in Scientific Tables[24]. The range for normal adults appears to be between 1.3m^2 and 2.5m^2, and the average male is considered to have skin surface area of 1.82m^2. For children, the lower limit of normal might be approximately 0.2m^2 (newborn).

Estimates of the fraction of skin exposed during different activities are given in

TABLE 9

EXPOSURE CHARACTERISTICS FOR DIFFERENT ACTIVITIES

Activity	Contributing Routes of Exposure	Fraction of Body Exposed	Duration of Exposure *	Frequency of Exposure	Population Exposed
Shower	Ingestion Inhalation Dermal absorption	1.0	15 minutes	3.5 per week	General
Shaving	Inhalation Dermal absorption	0.1	2 minutes	daily	Adult males
Laundry	Dermal absorption	0.8	Continuous	Continuous	General
Vehicle washing	Inhalation Dermal absorption	0.2	8 hours	Daily	Healthy adults
Miscellaneous Industrial	Inhalation Dermal absorption	0.1-0.2	Variable	Extended	Adults
Swimming	Ingestion Inhalation Dermal absorption	1.0	30 min-2 hrs.	Highly variable	General

* Single occurrence

Table 9. Two models for absorption of contaminants through the skin can be proposed. The first assumes absorption of the contaminant concurrently with the absorption of water (solution mechanism). The second assumes preferential absorption of the contaminant. Available data are limited and are insufficient to make a choice. One source[15] indicates that the steady state permeability of skin to water is relatively constant and in the range of 0.2-0.5 mg/cm^2/hr (or 3.6 to 9.1 g/hr for the whole body area). Another source[25] provides a somewhat higher figure, 1.5mg/cm^2/hr. A mathematical model of preferential absorption[19] is discussed in detail in Appendix A. It requires a value for the skin/solvent partition coefficient. Since these data are not generally available, it is suggested that values for other partition coefficients (e.g., mineral/water) can be substituted for the skin/solvent partition coefficient.

3. Duration of Exposure

Data on frequency of exposure and duration of each occurrence are not available for many of the potential recycle/reuse applications. Some values have been estimated[27] for swimming, shaving, etc. which correspond to activities of the general population. These data are summarized in Table 9.

4. Population Exposed

There are no available data on specific military populations involved in the identified activities. Some suggestions are included in Table 9.

V. DETERMINATION OF HEALTH EFFECTS

A. Initial Data Review and Selection

The data which are required as the basis for criteria formulation are described in this section. Further discussion of the difficulties in defining appropriate health effects data is provided in Appendix E.

According to the description of the reuse situation, data can be screened to select studies of the appropriate duration. For human exposures less than one week, acute toxicity data are appropriate. Many potential exposures at a permanent military establishment are of longer duration and the data selected should be derived from chronic toxicity data. For some applications, exposure routes are limited. For example, if inhalation of reused water is unlikely, the effects of respiratory exposure are unimportant. Further screening is provided by using a hierarchy of data selection and evaluation such as that shown in Figures 1, 2, and 3 which are appropriate for oral, respiratory and skin health effects, respectively.

Evaluation of Toxicity Data

Human data are the most desirable for predicting health effects in other humans. These data are sometimes available as a result of accidental, occupational or experimental exposure. Non-quantitative human data, descriptive or anectodal, is not particularly valuable, however, for establishing numerical limits of acceptable exposures. If quantitative aspects of the human data are deficient, experimental data resulting from animal observation are evaluated as illustrated in Figures 1, 2, and 3. Regardless of whether human or animal data sources are used, the same questions are relevant.

1. Is the dose quantitated (this information is essential for criteria development)?

2. Are there data concerning local binding and metabolism?

3. Are there local health effects data for this route of exposure?

4. Are there systemic absorption data from this route of exposure?

5. Are there distribution and elimination data associated with this route of exposure?

6. Are there systemic health effects data from this route of exposure?

All of these data are valuable for criterion development; some are optional. The quantitated dose is mandatory.

To establish a fully justified criterion which will include several simultaneous exposure routes, systemic absorption must be quantitated by a measure of plasma concentration of the water constituent in question. Data which demonstrate local and systemic health effects are necessary but often, the

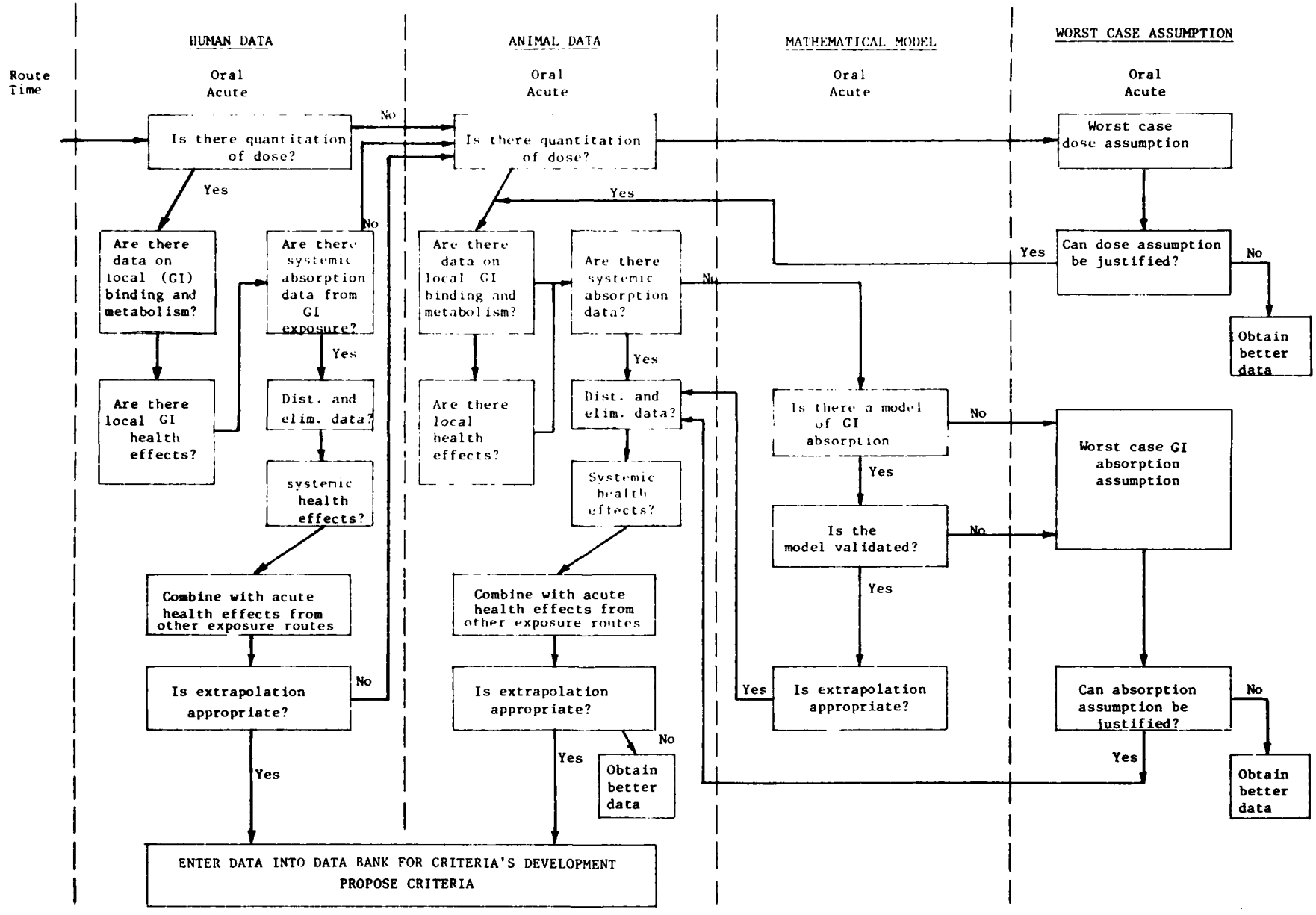

FIGURE 1. EXAMPLE PROTOCOL FOR EVALUATION OF TOXICITY DATA FOR ACUTE ORAL EXPOSURE

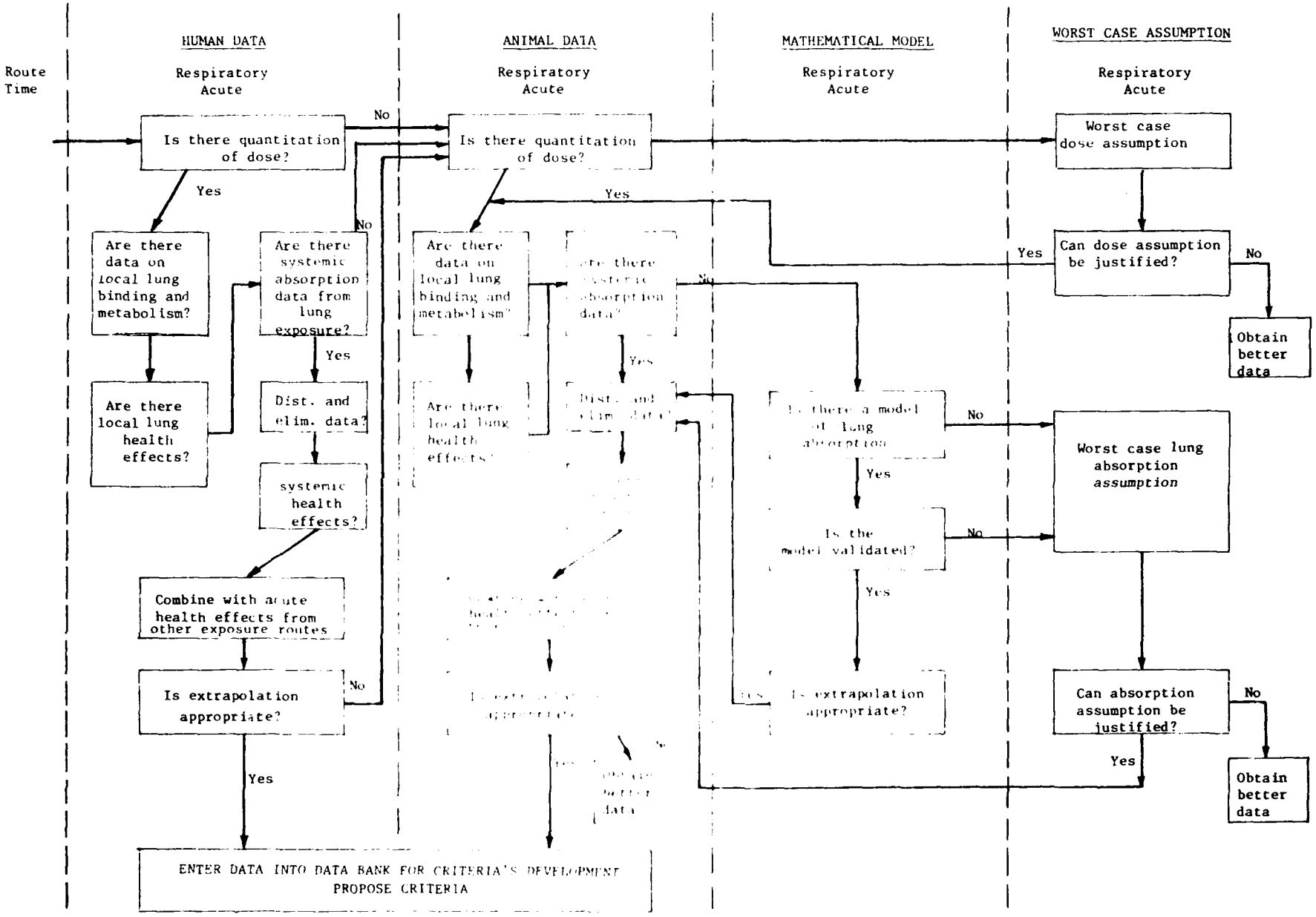

FIGURE 2. EXAMPLE PROTOCOL FOR EVALUATION OF TOXICITY DATA FOR ACUTE RESPIRATORY EXPOSURE

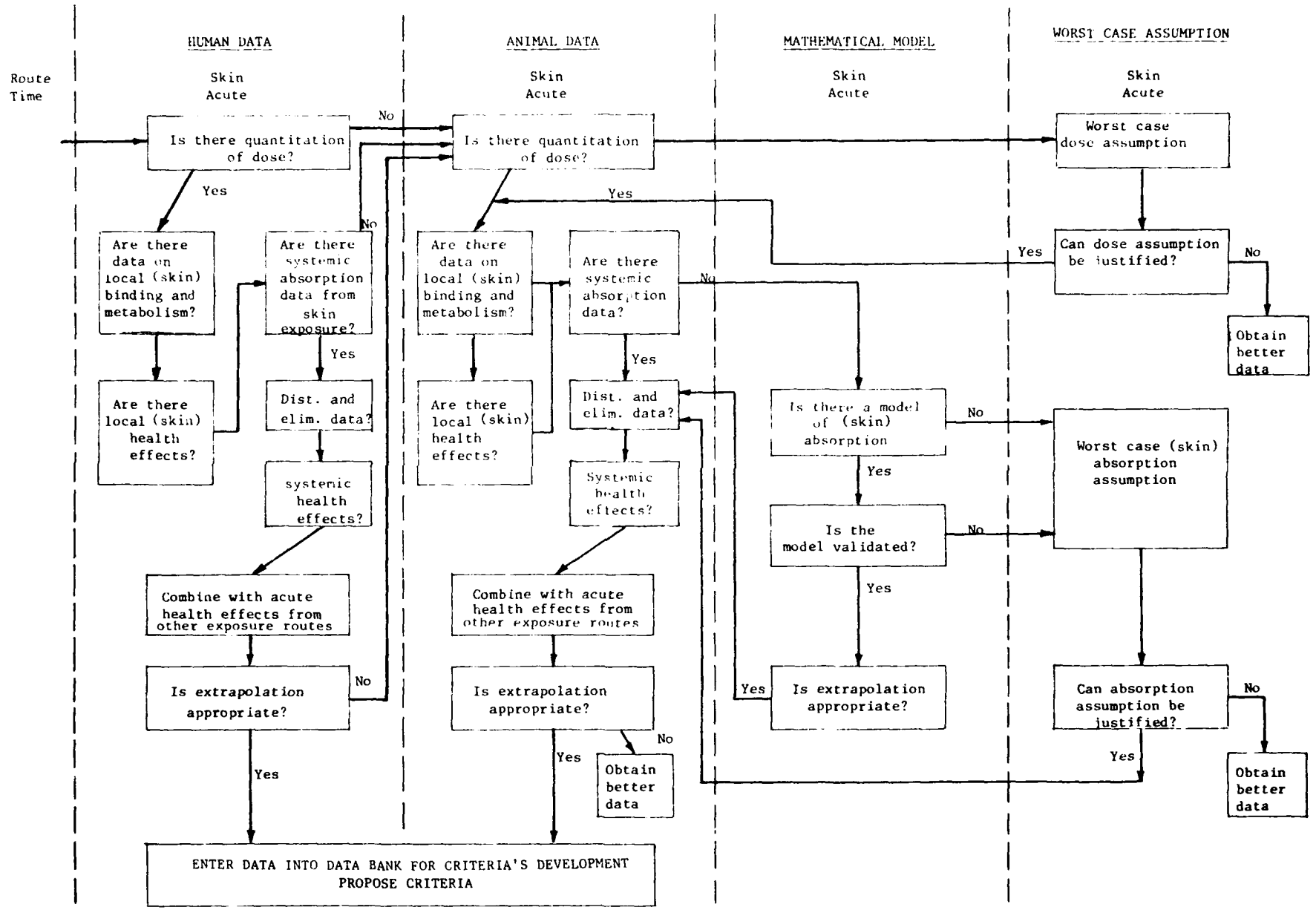

FIGURE 3. EXAMPLE PROTOCOL FOR EVALUATION OF TOXICITY DATA FOR ACUTE SKIN EXPOSURE

kinetics of binding, metabolism, distribution and excretion are unknown, and prediction of storage and buildup or chemical interaction is difficult. Some criteria values can usually be derived in the absence of such information.

For a local, site dependent effect, such as contact dermatitis, the final step is to carefully consider whether each individual data set can be appropriately extrapolated. There are some experimental protocols employing extreme conditions which simply will not apply to a military reuse situation. If extrapolation is considered inappropriate, new data must be obtained.

If several exposure routes are involved as in many reuse situations, the data for systemic absorption and effects are appropriately combined for consideration as a group. Before being entered into the data bank for criterion development, these data also must be carefully reviewed to check appropriateness to extrapolation.

In the event that local or systemic absorption data are not available for either human or animal studies, it may be possible to simulate this information via a mathematical model of complex physiological processes. Equations have been developed to describe skin penetration rates, behavior of particulates in the respiratory tract, distribution of orally administered drugs in the various compartments of the body, etc.

The problem with such models is that they frequently have not been rigorously validated by comparison of predicted results with measured results. Some measure of the reliability of the model prediction to the water reuse situation must be obtained before this information is used to predict human health effects.

Under some circumstances worst case assumptions may be justified. If a maximum or a minimum value can be specified, at least limiting values can be obtained. An example is the assumption that all inhaled particles are absorbed.

B. Pharmacokinetics and Toxicology

The data described in Figures 1, 2, and 3 are obtained from studies from several distinct disciplines, the principle ones being pharmacokinetics and toxicology. Current evaluation of the data requires expert judgement. Some of the considerations which are pertinent in the evaluation of the data of kinetics and toxicology are discussed below.

Pharmacokinetics is a study of the data which describe the time course of the entry of a material into the body, how it is metabolized, stored and excreted. It is this body of experimental evidence which allows predictions of human exposure levels on the basis of animal data. Kinetics are used to estimate rate of entry into the body through a limiting membrane. The nature of the membrane and the nature of the chemical must both be known if an administered dose is to be converted to an absorbed dose. Metabolism of a chemical may increase or decrease its toxic effect. Since metabolic conversions vary in importance and rate between animals and man, the particular pathway in the test animals must be compared to the pathway in man. If the two are comparable in both the test species and the human, direct extrapolation is acceptable. If the predominating

metabolic conversion is different, then animal data are used with much less confidence. Survival time of a chemical in the body is another factor for which kinetic data are required. If significant storage occurs, low concentration exposures can accumulate a significant body burden with prolonged exposure of sensitive tissues. In such a case, the acceptable human daily dose would be set at an extremely low level.

Excretion data describe the ultimate loss of a chemical or its metabolites. Once the route and metabolic pathways are established using an animal model, it is possible to judge whether the same mechanisms prevail in humans and whether the animal model allows extrapolation to humans. In addition, the excretory organs are at high risk and these data guide the search for the locus of toxic effect.

1. Routes of Entry

The total quantity impinging on the organism may not be directly related to the quantity or concentration of the material actually at the site or organ which is the locus of toxic effects. For example: suppose a compound causes severe pulmonary damage when present in the alveoli. If administration of 1 gram by aerosol is sufficient to cause adverse health effects, one-tenth of that dose given I.V. will accomplish the same. If the toxicant is administered by mouth, the adverse effects dose becomes 10 grams or more. The explanation is that I.V. administration is a direct route to the pulmonary bed with no possible detours and no problems of absorption. The aerosol, because of particle size differences, has low retention. The oral route, even with excellent absorption, directs materials to the liver where almost all of our hypothetical material is bound, metabolized and excreted via the bile. Thus, dose necessary to cause a measurable toxic effect will differ widely when the route of entry is varied.

The point of entry for each contaminant will usually sustain the highest exposure. Chemicals which are stored in a particular organ or tissue may be an exception because contaminants may accumulate by means of active transport to a concentration higher than that seen at the site of entry. High exposure at the entry may cause special problems. For example, irritants cause severe inflammation at the point of contact. In the lung, irritation will cause death at a dose tenfold lower than would occur with any other route of administration. Two factors are important: One, the high localized concentration, and two, sensitivity of the tissue. Thus, route of entry must be specified for prediction of possible damage.

The organ storing the highest concentration of the toxicant may not be the most susceptible organ. It may be quite unresponsive to the chemical being accumulated and the critical organ may not store the toxicant at all. In addition, the critical organ may vary with route of entry. High concentration, short duration exposures by inhalation may cause lung changes which are never observed with prolonged ingestion. This dependence of toxic effect on time, route and dose makes evaluation of potential toxicities more difficult.

2. Absorption Mechanisms

Absorption in the Gut. It is assumed that non-nutrient material will be absorbed through the gut in the same manner as drugs i.e., dependent on passive diffusion.

For fast diffusion, lipid solubility, small size and lack of ionization are all advantageous. Because of the responsive nature of the equilibrium system, a chemical in which as little as 0.1% is in the non-ionized form will be absorbed. The materials which do not pass through the limiting membranes are characterized as lipid insoluble, large in size and strongly ionized. Factors which cannot be predetermined will modify expected absorption rates. For example, gut flora, gut contents, gut pH, transit time, gut pathology and pre-existing blood levels of the constituent will modify entry of a material into the body through the GI tract. Because of differences between individuals and the differences within a single individual, the characteristic range of absorption for a given material may be very wide. It is not unusual for complete assimilation of the ingested material to occur.

In the gut, the site of absorption will differ with chemical structure. Weak acids or bases, being relatively undissociated, are well absorbed at a variety of pH's, and therefore absorption will occur in the stomach as well as in the small intestine. Stronger acids, which are dissociated at the pH found in the small intestine, will be absorbed more slowly there than in the stomach. The stomach, of course, is not a prime site for absorption because of its small surface area. A very good presentation of a mathematical model for calculation of absorption can be found in Reference 17 P. 143-149. As expected, the effects of biological factors of flora, and motility, etc., cannot be calculated.

An unusual observation has been made concerning the effect of concentration of the solution ingested. It has been documented that some weak acids, weak bases and poorly water soluble materials are absorbed faster (i.e., higher blood levels at early sampling time or more severe toxic effects) if the dose is administered in a larger volume of water. Increasing water volume, of course, results in lower concentration of administered solute. The apparent explanation is that the larger volume of water hastens stomach emptying and the drug comes into contact with the massive absorption surface of the small intestine earlier in the course of the exposure. It is also hypothesized that the increased water volume allows exposure of a larger percentage of the small intestine surface in addition to the earlier arrival. With a series of 12 drugs, the increase in water volume administered from 1.25% of body weight to 5% of body weight caused the number of deaths to increase from two to nine times.[28,29]

Absorption by Skin. The outer layer of the skin, the stratum corneum, is the main barrier to entry of materials. It is composed of membranes of dead cells, which polymerize to provide a highly resistant surface. The thickness of the stratum corneum differs over the body and, to some extent, the permeability of the skin is proportional to the thickness. Forehead, inner arm and scrotum are characterized by very thin stratum corneum and proportionally high permeability. Thick stratum corneum, however, does not guarantee extra protection. The palms of hands and soles of feet are 400 to 600 micrometers thick contrasted to 8 to 15 micrometers thickness in other parts of the body (back, arm). The nature of the polymer in these areas is quite different, in that it is to some degree water and base soluble. Entrance through intact skin of the palmar and plantar surfaces can be quite different from access through other regions of the integument.

Exposure to large amounts or to very toxic materials can, however, produce absorption of significant amounts of contaminant through normal skin. In addition, exposure to other chemicals including water may damage the skin or at least change its permeability characteristics, thus allowing entry of materials normally excluded.

The mechanisms of entry and the anatomical routes of entry into the skin are numerous, and a mathematical system which adequately predicts the quantitative behavior of chemicals which gain entry through the integument has not yet been devised. Water soluble molecules diffuse through the fibrous keratinized structure in the dead cells of the stratum corneum which can absorb 3 to 5 times their weight of water, increasing the access for polar molecules. Some materials which fail to gain entry into the body by diffusion through the fibers of the stratum corneum are still able to pass through the alternate pathways provided by sweat ducts, sebaceous glands, and hair follicles. These shunts provide a shorter path length between the surface and circulatory system, partly due to the extensive capillary system in contact with the various structures. Electrolytes may move preferentially through the skin of the appendages. Other materials which diffuse satisfactorily through the stratum corneum may enter more rapidly than expected in the preequilibrium stages due to short circuiting via appendages. The total contribution of skin appendages is modest because of small surface areas, but important because it increases greatly the difficulty of quantitative predictions.

There appears to be no specialized transport system to complicate the passage of material across the stratum corneum. In spite of its being nonliving, the stratum corneum is reactive in nature and physical principles which describe diffusion as directly proportional to concentration gradient and other fixed considerations are not necessarily predictive.

The models which exist do not allow for binding of differing species within the structure of the membrane or changes of the membrane itself as a result of wetting or exposure to solvents.

Aprotic solvents (donating protons to water or alcohol), such as DMSO, dimethylformamide or dimethyl acetamide can change the permeability of intact skin by a factor of 20, perhaps by changing the bond structure of water bound in the stratum corneum. The full effect of these chemicals requires a high concentration of the solvent, and the effect is usually reversible when the solvent is removed. Surfactants and detergents increase permeability by damaging the stratum corneum in a less reversible manner by changing the coiling of keratin filaments. Organic solvents damage skin in proportion to their lipid diffusibility. The removal of lipids from the stratum corneum leaves channels through which non-selective access occurs.

Key variables affecting the flux of pollutant through the skin are the concentration of pollutant in the water (for practical purposes, we can assume that the concentration of the pollutant in the body is zero, so that the flux is directly proportional to the pollutant concentration in the water), and the permeability constant of the solute. The membrane diffusion coefficient and the skin (membrane) thickness seem to be mutually dependent, so that the key variable may be the membrane (skin)/solvent (water) partition coefficient.

If data were available, this coefficient could be used to estimate the flux (effective dose rate) of pollutants. In limited literature search, few of the needed permeability or diffusion data were found to be available.

In the absence of a skin-water partition coefficient, solvent systems have been used as models. Examples are mineral oil-water, octanol-water, ether-water and chloroform-water. (See Appendix A.)

Materials compared by models using different solvent systems are sometimes ranked in the same order; however, the numerical predictions differ greatly. The majority of skin absorption modeling has been done in connection with drug development. As a result, there are data for some groups of closely related materials for which a particular model is highly predictive; however, no model has been validated over a broad range of unrelated chemical structures.

In addition, the questions of changing skin characteristics with inflammation, solvent exposure, solute loading, short circuiting via appendages, and variations in stratum corneum are not approached in any model. Skin absorption has not been a major consideration in most toxicity evaluations because other routes normally provide better access (lung), or invite higher doses (gut). As a result, tools for evaluation of skin as an entry site are somewhat primitive. In addition to permeability data, the state of the exposed skin is also important. Breaks in the skin, scratches, cuts, scabs, represent sites of easy entry for materials which might otherwise be excluded from the body in spite of extensive skin contact. The inflammatory process which accompanies rashes and sunburns characteristically includes increased permeability of tissues and high blood flow. Both of these factors can increase the penetration of the skin by chemicals by several orders of magnitude, (Ref.19). The exposure of the skin to a variety of chemicals may in fact change the characteristics of the skin itself.

Absorption by Inhalation. To estimate the dose of chemical received by inhalation, it is important to identify the form of the exposure. A vapor or gas will be absorbed into the body in accordance with the laws describing gas solubility and diffusion characteristics. If the gas is water soluble, a rather large percentage is removed from the air before actual contact with the lower respiratory tract, by absorption into the body from the naso-bronchial tree. For example, HCl causes severe lung damage if it reaches the lower respiratory system, but when HCl is inspired through the nose, the quantity which comes in contact with the alveolar tissue is small, because HCl gas dissolves in the moist surface of the nasal passages.

Insoluble gas easily reaches the alveoli and is distributed across the membrane according to gradient and blood flow. Absorption or elimination then is most directly dependent on circulation rate with very little relationship to respiratory volume. The soluble gas which reaches the alveoli on the other hand, is absorbed or eliminated in direct proportion to respiratory volume with very little effect from circulatory changes. The direction of diffusion, of course, is dependent on the gradient. (A good mathematical presentation of gas absorption can be found in Reference 30.)

For exposure to aerosols rather than gases, deposition, retention and absorption follow different patterns. Retention is dependent to a large extent on aerodynamic equivalent particle size (see Table 10). Particles in excess of 10μm are

TABLE 10

PERCENT RETENTION OF INHALED AEROSOL PARTICLES IN VARIOUS REGIONS OF THE RESPIRATORY TRACT

	Percent Retention									
	450 cm^3 Tidal Air					1500 cm^3 Tidal Air				
	20	6	2	0.6	0.2	20	6	2	0.6	0.2
Mouth	15	0	0	0	0	18	1	0	0	0
Pharynx	8	0	0	0	0	10	1	0	0	0
Trachea	10	1	0	0	0	19	3	0	0	0
Pulmonary bronchi	12	2	0	0	0	20	5	1	0	0
Secondary bronchi	19	4	1	0	0	21	12	2	0	0
Tertiary bronchi	17	9	2	0	0	9	20	5	0	0
Quarternary bronchi	6	7	2	1	1	1	10	3	1	1
Terminal bronchioles	6	19	6	4	6	1	9	3	2	4
respiratory bronchioles	0	11	5	3	4	0	3	2	2	4
Alveolar ducts	0	25	25	8	11	0	13	26	10	13
Alveolar sacs	0	5	0	0	0	0	18	17	6	7
Totals	93	83	41	16	22	99	95	59	21	29

The figures in the columns are percent retention; the column headings are particle sizes in micrometers. A 4 sec. respiratory cycle is assumed.

Source: Hatch and Gross, taken from table 3-4 in Principles of Drug Action: The Basis of Pharmacology, A. Goldstein, L. Aronow, S. Kalman, Wiley, 1974.

excluded, between 5μm and 2μm they are impacted in the upper respiratory tract and below 2μm are deposited in the alveoli. Much of the deposited material, however, is not retained in or absorbed by the lungs. The differences among individuals (anatomy and respiratory patterns) may result in a threefold difference in deposition rate. Particle deposition in the respiratory system at levels higher than terminal bronchiole will be dependent on air velocity, volume and particle size, but will generally not exceed 50%. Only about 20 percent of particles small enough to reach the alveoli are retained. There are two major clearance mechanisms: in the larger airways particles are removed promptly via mucociliary action. Particles have been typically observed to move up the respiratory tract at a rate of 7.3mm/minute and the mucociliary mechanism results in deposition of particles in the gut. In smaller divisions of the lung where cilia are not generally available to assist the removal of particles which deposit in the alveolar spaces, eighty percent are unmoved after 24 hours. The continued rate of removal after 24 hours is very slow and seems to be related to solubility. Half-lives of deposited material vary between 9 and 200 days and 50 to 100% of these materials ultimately dissolve. Particles may be engulfed and contributed to the mucociliary layer by macrophage migration. This would also contribute to alveolar clearance, but the collection of exogenous pigments in the alveoli of city dwellers and smokers leads one to the conclusion that the alveolar mechanism for clearance is not always adequate.

Cleared particles are removed from the lung and at least partly lost by expectoration and incomplete absorption from the gut. Limited studies indicate that particles deposited in the alveoli are more likely to be excreted through the urine, whereas residue from particles deposited in the ciliary pathway is more frequently found in feces. With the various clearance mechanisms determining site absorption and using a GI absorption of 5% of input, the total particulate (.1 to 10μm MMAD) absorption was calculated to range from 5 to 50% of inhaled amount.

Clearance rates are also greatly affected by some diseases such as asthma and by exposure to tobacco smoke or to anesthesia. Cillia so exposed fail to beat at the normal rate for prolonged time periods.

3. Metabolism and Storage

Toxic material may be metabolized by the liver into non-hazardous substances; conversely, compounds which are not toxic may be metabolized into toxic materials by the host. Differences in reaction rates in various species also account for many discrepancies in toxic effects in test animals. Metabolic products may be very reactive and frequently exert effects by interaction with host macromolecules. Generally, one can expect two stages in metabolism of extraneous organic materials. The first stage includes oxidation, reduction or hydrolysis, and the second state results in conjugation or synthetic products which tend to be polar and easily excreted via the kidney. There is a great variety of such processes, and they are generally unpredictable. Abstract modeling, which predict end products and reaction rates, is only valuable ex post facto.

Storage of toxic materials complicates the understanding of metabolism, because storage can occur in the critical organ, at the site of metabolism, or at the site of clearance.

Two major storage sites for lipid soluble materials in the body are the adipose tissue of the omentum and the subcutaneous layer of the skin. The quantities retained here will be proportional to lipid water partition coefficient and can be substantial in amount. The adipose tissue is not, in general, considered to be highly sensitive, but storage allows the option of a slow, sustained release and prolongs the duration of the exposure of those tissues which are more sensitive. Occasionally, rapid weight loss resulting from fasting causes mobilization of adipose tissue and sudden rapid release of toxic material stored in the fat cells. This has occurred with lipid soluble pesticides under unusual conditions.

Storage in bone is typical of a number of toxic materials. Chemicals are first incorporated in a loose association in the hydrated shell of a newly forming crystal structure. With time, this becomes a tighter binding and as inorganic material continues to be deposited, the earlier layers are covered and become unavailable for exchange. Until osteoclast activity solubilizes the crystal structure, the incorporated toxicant remains out of circulation and is probably not actively toxic. An excess of osteolytic activity can subsequently increase blood levels of the toxic chemical.

4. Excretion

Excretion of toxic materials is primarily effected by the kidney. All other secretory organs play the same role to some extent and for each toxic material there is a typical pattern of excretion. For example, bile secretion into the gut is important for DDT excretion. The alveolar structure is appropriate for loss of gaseous material whenever the concentration gradient allows.

Many toxic agents are very successfully metabolized and excreted in large amounts. If intake exceeds the capacity of the excretory system, if the metabolic process fails or if the primary excretory organ fails, the body concentration will increase and symptoms become manifest.

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VIII. APPENDICES

A. Technical Review of Skin Absorption

B. Bibliography of Absorption by the Skin

C. Contaminants Known to be Absorbed through Skin

D. Technical Review of Inhalation Exposure to Vapors of Contaminants in Water

E. Health Effects Data

APPENDIX A

Technical Review of Skin Absorption

It is frequently presumed that skin is an effective barrier to penetration into the body of substance in contact with the skin. However, there are important exceptions to this rule; for example, exposure to pesticides and to organic solvents. There has been some research in the area of skin absorption where the primary focus has been on the administration of therapeutic drugs by this route. This research had indicated that in many respects skin can be considered a biological membrane which behaves in an analogous manner to the lipid/protein membranes of all biological cells. Thus, the permeability of skin to a substance depends on the substance's partition coefficient between the membranes and the solvent (usually water). The flux, mass units/(unit area • unit time), depends on the concentration gradient between the surface of the skin and the blood circulating beneath the skin. These are principles of Fickian diffusion which have been very adequately developed for skin elsewhere (1,2,3,4). Mathematical models of human skin to predict permeability of a substance which have used Fickian diffusion principles and have incorporated measurements of the geometry of the stratum corneum of the skin have shown good correlation with in vitro and in vivo measurements of permeability to drugs having a wide range of lipid/water partition coefficients (4,5). Table A1 is data from the study by Michaels et al. (4). The partition coefficients for mineral oil/water have a range of almost six orders of magnitude and water solubilities of about 5 orders of magnitude. Note also that the water solubility is not closely correlated with the oil/water partition coefficient. Columns 6-8 give results of in vitro permeability determination. The authors point out that the variation in normalized flux ($\bar{J}$, more generally called permeability) for different compounds is much greater than the variation of permeability between skin samples for a particular compound; this means that a useful approximation of the permeability of human skin can be made which depends on the physico/chemical properties of the substance. The mathematical equation they derived is as follows:

$$J = Cp \times 0.135\ (\sigma D_L/D_p) \left[\frac{1.16 + 0.0017\ (\sigma D_L/D_p)}{0.16 + (\sigma D_L/D_p)}\right]$$

where J = Flux, $\frac{mg}{cm^2 \cdot hr}$

C_p = concentration in water, mg/ml

D_L/D_p = ratio of diffusivities of solute in lipid and in protein
≈ 0.002 for best fit to experimental data.

σ = partition coefficient in mineral oil/water.

Table A2 gives some estimates of the dose through skin at varying σ and at two concentrations. The surface area of the body is estimated to be 1.8 square meters.

TABLE AI

RESULTS OF EXPERIMENTAL AND PREDICTED VALUES OF NORMALIZED FLUX* FROM MICHAELS ET AL. (4)

Drug	Water solubility mg/ml at 30°C	Mineral Oil/water Partition Coefficient at 30°C	No. of Skin Donors	Number of Permeation Experiments	Range of Js(max) $\mu g/cm^2$ hr. at 30°C	Js(max) avg $\mu g/cm^2$ hr. at 30°C	Normalized Flux cm/hr x 10^3 Experimental	Predicted
Ephedrine	50	1.6	3	8	250 to 400	300	6.0	2.0
Diethylcarbamazine	800	0.064	2	6	83 to 120	100	0.13	0.13
Nitroglycerin	1.3	10	2	4	10 to 25	13	11	17
Scopolamine	75	0.026	5	10	2.0 to 8.0	3.8	0.05	0.05
Chloropheniramine	1.6	0.16	4	8	2.9 to 3.9	3.5	2.2	0.9
Fentanyl	0.2	200	5	10	0.8 to 3.8	2.0	10	112
Atropine	2.4	0.006	2	5	0.01 to 0.05	0.02	0.0086	0.012
Estradiol	0.003	12	4	8	0.01 to 0.03	0.016	5.2	20
Quabain	10	0.00026	2	4	0.005 to 0.02	0.008	0.00078	0.0005
Digitoxin	0.01	0.014	1	2	0.00012 to 0.00014	0.00013	0.013	0.027

*Normalized flux (J) times concentration in the water bathing the skin gives Flux, eg $\mu g/cm^2 \cdot hr$:

Normalized flux		Concentration		flux
$\frac{cm}{hr}$	X	$\frac{mg}{cm^3}$	=	$\frac{mg}{cm^2 \cdot hr}$

*Comparing J s permits one to ignore concentration difference

TABLE A2

HOURLY DOSE FROM TOTAL BODY EXPOSURE OF SKIN ESTIMATED FROM THE MODEL OF MICHAELS ET AL., 1975

Mineral Oil/Water Partition Coefficient	Water Concentration	Dose/hr.	
100	1 gm/l (1000 ppm)	1570.	mg
10	"	313.	
1	"	35.	
0.1	"	3.5	
1000.	1 mg/liter (1 ppm)	2.6	mg
100	"	1.6	
10	"	0.31	
1	"	0.035	

This model may only be useful if the mineral oil/water partition coefficient has been measured. Partition coefficients in other systems cannot be substituted to give a meaningful estimate. Table A3 demonstrates that the partition coefficients are only roughly parallel from one system to another for a group of compounds, and that absolute values differ greatly.

Because there is a wide variety of ways to determine the partition coefficient and because other parameters (e.g., temperature) affect the distribution between the two immiscible liquids, the values found often show variability among investigators as well. The model suggests that compounds with low solubility in water and good solubility in organic liquids should be absorbed through the skin to a significant degree. Many pesticides and organic solvents do readily penetrate skin and cause toxicity. Table 4A lists some organic solvents and pesticides with high partition coefficients in octanol/water. It is estimated that the octanol/water partition coefficient is 100 to 200 times the mineral oil/water partition coefficient. Table A3 indicates that for a group of dissimilar compounds, the correlation between the two systems may be quite poor, however.

The most important shortcoming of this model is that it cannot adjust for interactions between solutes and the skin; the model assumes that the properties of the skin do not change as a consequence of exposure to any of the solutes. In most cases where skin properties may be modified, its permeability to solutes increases. Skin is made more permeable by concomitant treatment with surfactants (6). If skin is completely defatted by organic solvents the permeability to other solutes can be increased 2-3 orders of magnitude (7). Some solvents may severely disrupt the architecture of the stratum corneum and cause a large increase in permeability (8). Thus, the precision with which the model could actually predict the exposure dose under highly variable conditions could be very poor. Nevertheless, the model has some utility in indicating which pollutants could present problems under water use conditions allowing prolonged and/or large skin surface exposure.

TABLE A3

COMPARISON OF PARTITION COEFFICIENTS IN DIFFERENT SYSTEMS

Compound	Ether/Water	Olive Oil/Water
Urea	0.0005	0.032
Methyl Urea	0.0012	0.05
Dimethyl Urea	0.0116	0.3
Diethyl Urea	0.0185	0.63
	Chloroform/Water	**Heptane/Water**
Barbital	0.7 (2.0)*	<0.001 (.005)
Secobarbital	23.3	0.1
Thiopental	>100. (102)	3.3 (.95)
Phenol	2.3	0.15
Toluidine	97.5	3.3
Aniline	26.4 (17)	1.1 (0.55)
n-nitroaniline	39.2	0.24
p-nitroaniline	19.8	0.13
Antipyrine	28	0.04
Aminopyrine	73	0.15
Theophyline	0.3	0.02
	Octanol/Water	**Mineral Oil/Water**
Estradiol	490	12
Fentanyl	224	200
Atropine	63	.006
Scopalamine	17	.026
Ephedrine	~10	1.0
Trichloroethylene	195	34.4 (fat at 20°C) 320 oil at 37°C
Chloroform	93	70 unspecified type

*Values in parenthesis are from different sources to indicate the variation in measurement by different investigators.

TABLE A4

OCTANOL/WATER PARTITION COEFFICIENTS FOR SOME POLLUTANTS

Pesticides	Partition Coefficient
Malathion	780
Aldrin	1020
Paraquot	100,000
Organic Solvents	
Methylene Chloride	18
Chloroform	93
Trichloroethylene	195
Tetrachloroethylene	400-759
Tetrachlorobenzene	
1,2,3,4 1,2,3,5 1,2,4,5	~ 35,000

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APPENDIX B

Bibliography on Absorption by the Skin

1. Characteristics of Agent

- Chemical Composition
- Physical Characteristics
- Stability
- Solubility in Body Fluids
- Interaction Between Agents

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- Site of Contact

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- Length and Frequency of Exposure
- Time of Exposure (e.g., summer vs. winter, day or night)

3. Characteristics of Subject

- Species

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APPENDIX C

Contaminants Known to be Absorbed Through Skin

ACETONITRILE
ACROLEIN
ACRYLAMIDE
ACRYLONITRILE
ALDRIN
ALLYL ALCOHOL
ALLYL CHLORIDE
ALLYL GLYCIDYL ETHER
4- AMINODIPHENYL
2-AMINOPYRIDINE
n-AMYL ACETATE
ANILINE
ANISIDINE
ARSENIC (and compounds)
AZINPHOSMETHYL
BENZENE
BENZIDINE
BIS(CHLOROMETHYL) ETHER
BROMOFORM
n-BUTYL ALCOHOL
BUTYLAMINE
BUTYL CELLOSOLVE
CARBARYL
CARBON DISULFIDE
CARBON TETRACHLORIDE
3,3-DICHLOROBENZIDINE
DICHLOROETHYL ETHER
DICHLORVOS
DIELDRIN
DIETHYLAMINOETHANOL
DIGLYCIDYL ETHER
CHLORDANE
CHLORINATED DIPHENYL OXIDE
CHLOROACETALDEHYDE
O-CHLOROBENZYLIDENE MALONONITRILE
CHLOROBROMOMETHANE
CHLORODIPHENYL, 42 PER CENT CHLORINE
CHLORODIPHENYL, 54 PER CENT CHLORINE
CHLOROPRENE
COAL TAR PITCH VOLATILES
CRESOL (all isomers)
CUMENE
CYANIDES (ALKALI)
CYCHLOHEXANOL
CYCLOHEXANONE
CYCLOPENTADIENE
DDT
DECABORANE
DEMETON
DIACETONE ALCOHOL
DIAZOMETHANE
1,2 DIBROMO-3-CHLOROPROPANE
DIBUTYL PHTHALATE
o-DICHLOROBENZENE
p-DICHLOROBENZENE
ETHYLENEIMINE
N-ETHYLMORPHOLINE
FORMALDEHYDE
FURFURAL
FURFURYL ALCOHOL
HEPTACHLOR

DIISOPROPLAMINE
DIMETHYLACETAMIDE
DIMETHYLANILINE
DIMETHYLFORMAMIDE
1,1-DIMETHYLHYDRAZINE
DIMETHYL SULFATE
DINITROBENZENE (all isomers)
DINITRO-o-CRESOL
DINITROTOLUENE
DIOXANE
DIPHENYL
DIPROPLENE GLYCOL METHYL ETHER
ENDRIN
EPICHLOROHYDRIN
EPN
EPOXY RESINS
2-ETHOXYETHANOL
2-ETHOXYETHYL ACETATE
ETHYL ACRYLATE
ETHYLBENZENE
ETHYL CHLORIDE
ETHYLENE CHLOROHYDRIN
ETHYLENE DIBROMIDE
ETHYLENE DICHLORIDE
ETHYLENE CLYCOL DINITRATE/ NITROGLYCERIN
MEVINPHOS
MONOMETHYLANILINE
MONOMETHYLHYDRAZINE
MORPHOLINE
NALED
NICOTINE
p-NITROANILINE
NITROBENZENE
HEXACHLOROETHANE
HEXACHLORONAPHTHALENE
HYDROGEN CYANIDE
ISOPROPYL ALCOHOL
KEPONE
LINDANE
MALATHION
MERCURY
MERCURY (alkyl compounds)
MESITYL OXIDE
METHYL ACRYLATE
METHYL ALCOHOL
METHYL BROMIDE
METHYL BUTYL KETONE
METHYL CELLOSOLVE
METHYL CELLOSOLVE ACETATE
METHYLCYCLOHEXANOL
o-METHYCYCLOHEXANONE
4,4'-METHYLENEBIS (2-CHLOROANILINE)
METHYLENE CHLORIDE
METHYL FORMATE
METHYL IODIDE
METHYL ISOBUTYL CARBINOL
METHYL ISOCYANATE
METHYL PARATHION
TETRAETHYL DITHIONOPYROPHOSPHATE
TETRAETHYLLEAD
TETRAETHYL PYROPHOSPHATE
TETRAMETHYLLEAD
TETRAMETHYLSUCCINONITRILLE
TETRYL
THALLIUM
TIN (organic compounds)
TOLUNE

p-NITROCHLOROBENZENE
N-NITROSODIMETHYLAMINE
NITROTOLUENE
OCTACHLORONAPHTHALENE
PARAQUAT
PARATHION
PENTABORANE
PENTACHLORONAPHTHALENE
PENTACHLOROPHENOL
PERCHLORYL FLUORIDE
PHENOL
p-PHENYLENEDIAMINE
PHENYLHYDRAZINE
PICRIC ACID
beta-PROPIOLACTONE
n-PROPYL ALCOHOL
PROPYLENE IMINE
PROPYLENE OXIDE
n-PROPYL NITRATE
PYRIDINE
SODIUM FLUOROACETATE
STYRENE
TELLURIUM
TETRACHLOROETHANE
TETRACHLORONAPHTHALENE
o-TOLUIDINE
TOXAPHENE
1,1,1-TRICHLOROETHANE
1,1,2-TRICHLOROETHANE
TRICHLORONAPHTHALENE
1,2,3-TRICHLOROPROPANE
TRI-o-CRESYL PHOSPHATE
2,4,6-TRINITROTOLUENE
TURPENTINE
WARFARIN
XYLENE
XYLIDINE

Source: Chemical Hazards of the Workplace. Proctor & Hughes, Lippincott, 1978.

APPENDIX D

Technical Review of Inhalation Exposure to Vapors of Contaminants in Water

The effective dose rate by inhalation (U_v) is a product of the air concentration of the contaminant (C_{pair}), the ventilation rate (VR), and the respiratory retention factor for the contaminant, i.e.,

$$U_v(\text{liters/min}) = C_{air} \times VR \times \text{Retention Factor}$$

If we assume conservatively that all of the substance inhaled is absorbed, then retention factor is 1.0. Ventilation rate varies widely with the level of physical activity. A moderate work activity demands a ventilation rate of approximately 20 liters per min, but actual ventilation rate ranges from about 7 liters/min. at rest (e.g., sleeping and sitting quietly) to 50 liters/min. during strenuous physical activity. The combined uncertainty from the retention factor and ventilation rate is approximately 1.5 orders of magnitude.

For dissolved gases in solution, or for dilute solutions of a volatile solute in a solvent, Henry's law states that the partial pressure of the solute in the gas phase is directly proportional to the concentration in the solution or:

$$P_p = K_H C_p \qquad [1]$$

where: P_p = partial pressure of contaminant in the gas phase (atm)
K_H = Henry's law coefficient
C_p = concentration of contaminant in the liquid phase (mg/l)

Although this law would hold for most of the contaminants dilute solution, there are only few data available applicable for Henry's law coefficients. However, a value for Henry's law coefficient can be derived using Raoult's Law which states:

$$P_p = P_t Y = \gamma P_{vp} X \qquad [2]$$

where: P_t = total pressure of the gas phase (usually one atm in this analysis) (atm)

P_{vp} = vapor pressure of the pure contaminant at the system temperature (atm)

Y = mole fraction of contaminant in the vapor phase

X = mole fraction of contaminant in the liquid phase

γ = activity coefficient of contaminant in solution (usually assumed to be unity in dilute solution)

Further,

$$X = \frac{C_p / M_p}{C_p / M_p + C_w / M_w} \qquad [3]$$

where: C_w = concentration of water = 1000 mg/liter

M_p, M_w = molecular weight of contaminant and water (18) respectively

because the solution is dilute $C_p/M_p < C_w/M_w$

$$X \approx \frac{C_p/M_p}{C_w/M_w} = \frac{C_p.0.018}{M_p} \quad [4]$$

It follows that

$$P_p = \frac{P_{vc}.C_p.0.018}{M_p} \quad [5]$$

The concentration of the contaminant in air (C_a) is related to the partial pressure by the ideal gas law

$$P_p = \frac{C_{air}RT}{M_p} \quad [6]$$

$$C_{air} = \frac{P_{vp}.C_p.0.018}{RT} \quad [7]$$

where: C_{air} = concentration of contaminant in air (mg/l)

R = 0.082 liter atm deg.$^{-1}$ mote^{-1}

T = Absolute temperature (usually about 300°K)

Simplifying equation 7:

$$C_{air} = 7.4 \times 10^{-4} \; P_{vp}.C_p \qquad (P_{vp} \text{ in atm}) \quad [8]$$

Usually P_{vp} is quoted in mmHg (1/760 atm):

$$C_{air} = 9.7 \times 10^{-7} \; P_{vp}.C_p \qquad (P_{vp} \text{ in mmHg}) \quad [9]$$

The amount absorbed by inhalation of vapor is:

$$U_v = C_{air} \times VR \times \text{exposure time} \quad [10]$$

$$U_v = 9.7 \times 10^{-7} \; P_{vp}.C_p \times VR \times \text{exposure time} \quad [11]$$

This approximation is used in the calculations given in chapter III.

APPENDIX E

HEALTH EFFECTS DATA

Health effects data are particularly difficult to deal with because these effects range from slight irritation during contact to malignant carcinoma twenty years later. Any biochemical process or anatomical structure of body may be the locus of toxic effect. There is as yet no effective way to predict these effects. Lethal, chronic, irreversible or progressive changes are considered more important, but short-term acute changes may have important consequences to the military organizations.

A full evaluation of toxic manisfestations requires a comprehensive study of animals exposed to a particular chemical. This is complex because of the wide variety of systems which must be evaluated. For example, the effect of a chemical which results in irregularities of the heartbeat will remain unknown until EKG studies of the exposed animal are conducted. Rodent EKG measurement is not a usual screening device and this effect may remain unknown in spite of a comprehensive study of the test system. Such an effect which has no anatomically visible lesion, may well be first identified from anecdotal human reports.

Intensive investigation of health effects of a chemical first results in a list of anatomical and physiological changes following acute, high dose administration. This list gives direction to the study of lower dose levels. Thus, if a high dose results in acute necrosis of cortical nephrons, one looks for signs of renal disease following administration of lower doses over different time periods. When a complete list of physical findings has been assembled, symptoms indicative of toxic effects must be distinguished from physical changes which have no known consequence. Criteria for permissible human exposure levels are then set at a level which will avoid a specific toxic symptom.

A comprehensive dose range study using the chosen route of entry and duration of treatment relevant to a specific water reuse activity is desirable. Limited studies of very sensitive systems (liver, blood forming organs, skin, eyes) are more frequently available. Criteria developed from such limited data generally incorporate a safety factor to reflect a lower confidence level. A frequently accepted assumption is that a chronic exposure having no negative consequences is also safe for shorter (acute or subchronic) exposures.

If, however, the only available data pertain to lethal dose levels, predictions of safe exposure cannot be made. There is no fixed relationship between the amount of chemical causing death and the amount causing a sub-lethal effect, so that one cannot readily set standards by a mathematical construct such as "lethal dose divided by 10". Some data analysis [1] has shown that animal acute lethal dose divided by 100,000 has a very high probability of being safe for humans. However, the resulting safe level may be too low to be useful.

Health Effects with Unusual Dose Related Effects

Special health effects which fail to follow the simple relationships between dose and response are allergy, carcinogenesis, birth defects and micro-biological contamination. Some of these problems are discussed below.

1. Allergy

There are little data concerning the allergenic potential of water contaminants in general, or the fraction of the population in which allergies are manifest. Possibly 50% of the population suffers from allergic reactions at some time, but minor allergic reactions which are a nuisance tend to be unreported. In the absence of data it becomes very difficult to evaluate the natural history (frequency, severity, progression) of the allergic response. Chronic low level exposure to allergenic xenobiotic materials would be expected to promote development of allergies in an exposed population.

The most comprehensive data on allergic reactions is available for the drug penicillin. [2] Several studies have been conducted indicating allergic reaction in 1 to 10% of the population under treatment. Recurrent treatment with the same drug increased incidence of allergic responses. In a study of sulfonamides, allergic responses were observed in 5% of the patients during the first course of treatment, and 11% during a second treatment. In the subgroup which reacted to the first treatment, the second course of therapy resulted in allergic responses in 69%. Extensive evaluation of the data indicates that allergy is the result of interactions between genetic predisposition, exposure frequency, site of contact, the chemical structure and exposure to other similar chemicals with cross reactivity. Skin exposure more often results in sensitization than does oral exposure.

Almost 20% of industrial dermatitis is allergic in nature, an estimated 120,000 cases/year. After initial sensitization, the allergic response is triggered by low levels of exposing agent. Thus, the low levels of antigen encountered in water are not any assurance of protection. There is evidence that protein molecules represent the best allergen; the absence of protein in a chemical exposure gives no guarantee of safety. Very small molecules are frequently able to act as haptens by linking in vivo to proteins provided by the victim. The most effective of the non-protein allergens are those which are able to form covalent bonds at physiological pH and which were not metabolized rapidly.

The state of understanding of the sensitization process and the allergic response does not permit quantitative treatment, and development of methodology encompassing allergic responses in connection with military recycle/reuse applications is beyond the scope of this study.

2. Carcinogenesis

The current body of U.S. Federal regulations is based upon the premise that carcinogenesis does not have a safe threshold. Every exposure entails some risk. Therefore, no safe dose (NOEL) can be identified. One approach[3] is to specify the increase in the number of cases (1 in 10^5, 1 in 10^6 etc.), which might be acceptable, and define the criteria based on that dose level.

3. Birth Defects

The state of the art with regard to chemical induced birth defects is primitive. Responses of closely related species are inconsistent and predictions from animal to man are poor. Severity of effect is frequently related to time of dosing rather than dose itself. This important toxic manisfestation will require special consideration and is beyond the scope of this study.

4. Microbiological Health Effects

In contrast with other health effects data which are considered according to individual chemical, microbiological quality criteria for water have traditionally considered only total coliform levels. The safety of water for drinking, swimming and shellfish harvesting continues to be regulated by such guidelines in spite of the growing awareness that total coliforms may not be adequate indicators of all human pathogens (e.g., viruses) and therefore do not reliably predict all human pathogen levels in all types of water.

Unique factors that must be considered in water recycle/reuse applications are that (1) water alone can serve as a growth medium for many genera of bacteria including Pseudomonas, Enterobacter, Streptococcus, Achromobacter and Escherichia, (2) development of resistance to antimicrobials and antibiotics and adaptation to adverse growth conditions are rather common among microorganisms (especially the Pseudomonads), and (3) current disinfection practices which might be applied in water reuse situations are designed to eliminate waterborne bacterial diseases and may not kill all viruses.

Thus, it is difficult to quantitate the dose of the microbiological agent because it changes with time. An awareness of the uncertainties of using coliform (fecal or total) as the sole criterion for reclaimed wastewater for agricultural use is evident in the Utah State Division of Health Guidelines [4] proposed in 1977. In these guidelines, reclaimed wastewater is considered suitable for application by surface or spray irrigation to forage crops for animal feed if it contains no more than 200 fecal coliforms/100 ml or 2000 total coliforms/100 ml, provided there is no public access to such agricultural sites. Alternatively, waters for forage crops for animal feed may contain 20 fecal coliforms/100 ml or 200 total coliforms/100 ml, and if the water is sprayed, a 1000-foot buffer zone must be provided. For application to parks, golf courses, and lawns, and in industrial areas, the Utah guidelines would permit only one total coliform/100 ml (meets microbiological standards for primary drinking waters). Non-potable water quality is thus described by an adaptation of the primary drinking water standards with an in-use restriction (no public access or a buffer zone) intended to protect people from infection by routes of exposure other than ingestion (skin, inhalation).

Potentially, the greatest health hazard associated with water reuse is from inhalation of aerosols containing pathogens, rather than from ingestion, because the upper respiratory tract is more vulnerable to infection by foreign microorganisms than is the gut. Skin exposure can be an important route of infection if cuts and abrasions exist. Infection of the eye would be a possible concern with certain kinds of microorganisms. Data on dose response relationships are very limited for waterborne viruses and bacteria ingested orally and are virtually nonexistent for inhalation, skin exposure or eye exposure.

For adaptation of traditional water quality standards to water reuse applications, two problems have to be investigated. The validity of using coliforms, as indicators of human pathogens in water reuse applications must be proven. Secondly, the feasibility of extrapolating safety criteria to routes of exposure other than ingestion must be explored. No microbiological profile of waters being considered for reuse exists to help answer the first question, and few data available to answer the second. Thus, development of water criteria data base and methodology cannot be accomplished at present.

Safety Factors

Safety factors are generally used when extrapolating data from limited studies to the general population. Typically, genetic differences of an order of magnitude exist between the most and least sensitive members of a population. Extrapolation between species, e.g., laboratory animals and humans requires consideration of the heterogencity of the human population. Finally, the laboratory work on the toxicity of single chemical does not take into account synergistic effects caused by other chemicals which may be present in the environment.

To compensate for these uncertainties the EPA has developed a protocol in the Water Quality criteria documents which defines uncertainty factors, [5] as follows:

	Data Base	Uncertainty Factor
1.	Valid experimental results from studies on prolonged ingestion by man, with no indication of carcinogencity.	10
2.	Experimental results from studies of human ingestion not available or scanty (e.g., acute exposure only). Valid results of longterm feeding studies on experimental animals or in the absence of human studies, valid animal studies on one or more species. No indication of carcinogencity.	100
3.	No long-term or acute human data. Scanty results on experimental animals. No indication of carcinogencity.	1000

These uncertainty factors are used in every case as a divisor of the highest reported long-term dose which is observed not to produce any adverse effect.

These are appropriately described as uncertainty factors rather than safety factors because they pertain to the likelihood that the data will be shown to be reproducible. A chemical is severely penalized because of scant data not because of ominous findings. There is also some concern about the subtlety of end points which would be considered sufficient. For example, a well executed long-term feeding study might use death as the adverse effect. The highest dose which failed to cause dealth would be considered to be a no adverse effect dose simply because no additional measurements were taken. It is highly likely that adverse effects could be identified at much lower doses had the experiments been conducted using a different end point.

This protocol provides a basis for developing safety or uncertainty factors for military recycle reuse applications, but different numerical values may be appropriate because of differences in observed effects, exposure routes, population, etc.

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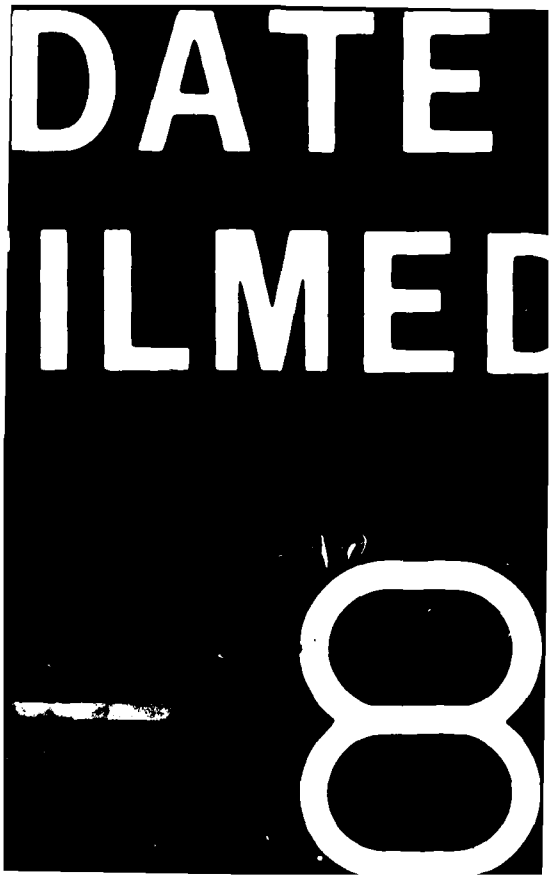
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